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The Journal of Laboratory and Clinical Medicine

VOL. II. ST. LOUIS, FEBRUARY, 1917 NO. 5.

ORIGINAL ARTICLES

FURTHER STUDY OF THE HISTOPATHOLOGY OF THE AUTONOMIC NERVOUS SYSTEM IN GOITER*

BY LOUIS B. WILSON, M.D., ROCHESTER, MINN.

WITH A NOTE ON THE SPECIAL TECHNIC OF RECONSTRUCTIONS AT HIGH MAGNIFICATIONS.

BY THOMAS O. YOUNG, B.S., MINNEAPOLIS, MINN.

MANY of the older clinical writers classified exophthalmic goiter as a disease of the sympathetic nervous system. It is only in recent years that the primary importance of the thyroid has become recognized. Although we must give full weight to overfunction of the thyroid as the direct cause of hypermetabolism, which is the dominant factor in the syndrome designated "exophthalmic goiter," yet it must be confessed that when we attempt to explain the primary cause of overfunction of the thyroid, all our hypotheses are unsatisfactory.

Cannon[1] has shown that by the constant stimulation of the thyroid produced by anastomosing the phrenic nerve with fibers of the cervical sympathetic, he has been able to produce many of the symptoms of hyperthyroidism. McCarrison[2] has adduced a large mass of data, both clinical and experimental, supporting the hypothesis that both simple and exophthalmic goiter are due to water-borne infection. However, the theory that the thyroid is excited beyond its normal function by infection within the gland has received little supporting evidence in the bacteriologic findings, in the histologic appearance of local inflammation, or in the clinical course of the disease.

Some time ago in an examination of the changes in the various skeletal muscles in cases of exophthalmic goiter, I was struck by the extremely erratic distribution of the degeneration in the various muscle fibers and bands. Such

*Presented before the Minnesota State Medical Association, Minneapolis, Oct. 12, 1916.

an erratic distribution is difficult to explain on any theory of work-change or of the irregular vascular distribution of a blood-borne toxin. On the other hand, it might readily arise from the irregular destruction of selected neurons, or portions thereof, controlling various muscle bundles. In consideration of these facts from the clinical, experimental, bacteriologic, and histologic standpoints I was led to investigate more carefully the histopathology of the autonomic nervous system in relation to goiter.

PREVIOUS REPORTS IN THE PRESENT SERIES OF OBSERVATIONS.

Durante and I[3] have recently reported our observations on twenty superior cervical sympathetic ganglia removed at operation from sixteen patients with hyperplastic toxic (exophthalmic) goiter. Our findings may be briefly summarized as follows:

1. Definite histologic changes in the cells of the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goiter occurred in all cases examined.

2. These histologic changes consisted of various stages of degeneration: namely, (a) hyperchromatization, (b) hyperpigmentation, (c) chromatolysis, and (d) atrophy or (e) granular degeneration of the nerve cells.

3. Some of the ganglia contained cells resembling the partially differentiated cells found in the ganglia of infants.

4. Accompanying the more advanced changes in the ganglion cells were similar degenerative changes in the nerve fibers and an increase of connective tissue throughout the ganglion, but especially in the outer and middle coats of the vessels and in the periganglionic tissue.

5. So far as could be determined from the small number of observations, the pathologic changes in the cervical sympathetic ganglia were parallel to the stage and intensity of the symptoms of hyperthyroidism and to the hyperplastic and regressive changes in the thyroid.

In addition to the above, I have recently reported[4] my observations on a study of the cervical sympathetic ganglia removed at autopsy from twelve patients dying during the course of exophthalmic goiter, the observations on which were controlled by similar studies on sympathetic ganglia removed at autopsy from patients dying of diseases other than exophthalmic goiter and by studies of Gasserian ganglia removed at operation from patients with trifacial neuralgia. The results of these latter studies show that the changes in the ganglia cases of exophthalmic goiter coming to autopsy are parallel in all respects with those in the ganglia removed at operation, while the ganglia removed from patients coming to autopsy from other diseases and the ganglia removed at operation for conditions other than exophthalmic goiter furnish valuable negative controls. In the latter report I have also included a brief preliminary note of experimental work in the production of the degenerative changes in the ganglionic cells. In one animal (goat) lesions parallel with those in the cervical ganglia removed from patients with acute exophthalmic goiter were produced by the injection into the capsule of the ganglion of a virulent culture of Bacillus bronchisepticus, the bacillus associated with canine distemper. This experimental work is still in progress, and will be made the subject of a subsequent report.

SUBJECT MATTER OF PRESENT STUDY.

I wish to present more in detail and from a different viewpoint the general character of the histologic lesions. The study of these turns on the irregularity of their distribution, their extent, and the probable order of the various phases of degeneration.

When one studies the pathologic changes in isolated sections of the ganglia, it is difficult to determine the exact distribution of affected cells, though even in studying nonserial sections he is struck by the presence of apparently perfectly normal cells in immediate apposition to others that appear to be in advanced stages of degeneration. Since, however, the ganglion cells are of much greater diameter than the thickness of good paraffin sections, it is possible to interpret the apparent irregularities in size and irregular distribution of pigment in the ganglionic cells in a single section on the theory that they are the result of oblique cuts including only small portions of cells. In order, therefore, to determine the extent of the destruction of the cells one must study series of sections at least of sufficient extent to include all portions of a group of ganglionic cells selected in a given microscopic field in a section near the middle of the series. All preceding and succeeding sections in which these individual cells appear must be studied. I recognized this principle early in the work and all material has been studied in such serial preparations. One is able thus to demonstrate beyond a doubt the character and extent of the changes in a given group of ganglion cells.

This summer, Mr. T. O. Young, a medical student in the University of Minnesota, under my direction has prepared a number of Born wax reconstructions of groups of cells selected as above indicated. A description of his technic is herewith appended.

All the reconstructions were made at a magnification of 600 diameters, and photographed down to a magnification of 300 diameters, at which magnification they are herewith reproduced. In examining them the fact must not be lost sight of that they represent groups of cells selected as above indicated: i.e., those of each of which some portion appears in a single section of the series; thus while all portions of each cell in the group is shown, the group itself covers the distribution of the cells in 2 dimensions only. The interior details of the cells can, of course, be represented in the opaque models only diagrammatically and by arbitrary signs. With these, however, and the knowledge that the relative shape and size of the cells has been preserved, the analysis is interesting.

PROTOCOLS.

Case I.—A-153535, Fig. 1. (For previously reported details of this case see Case II in article Ref. 4.) This reconstruction is from a group of ganglion cells in the left superior cervical sympathetic ganglion of a female 19 years of age who had had severe symptoms of exophthalmic goiter for five months. Of the nine cells shown, four, A, B, C, and D, are apparently normal and five, E, F, G, H and I are pigmented. In one, I, the most pigmented, the nucleus has disappeared; in the other eight the nuclei show no changes of sufficient importance to warrant our designating them as degenerated.

Fig. 2. This reconstruction is from another area in the same ganglion as that shown in Fig. 1. In this area, three cells, A, B, and C, are apparently normal and four, D, E, F, and G, are pigmented. In two, D and E, the nuclei

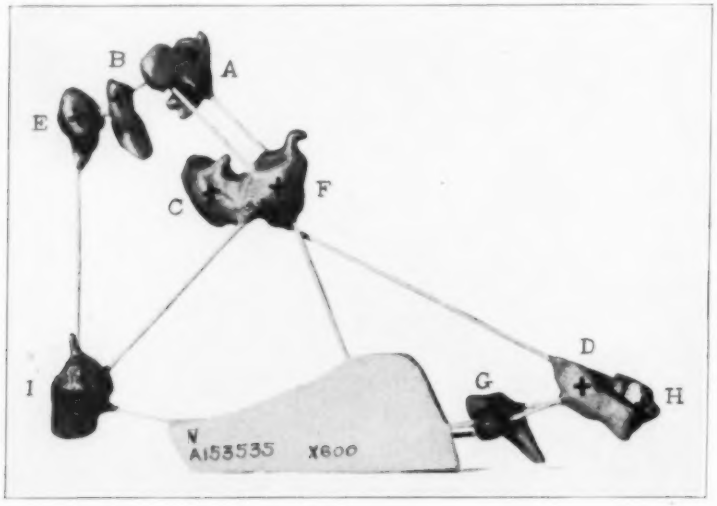


Fig. 1.

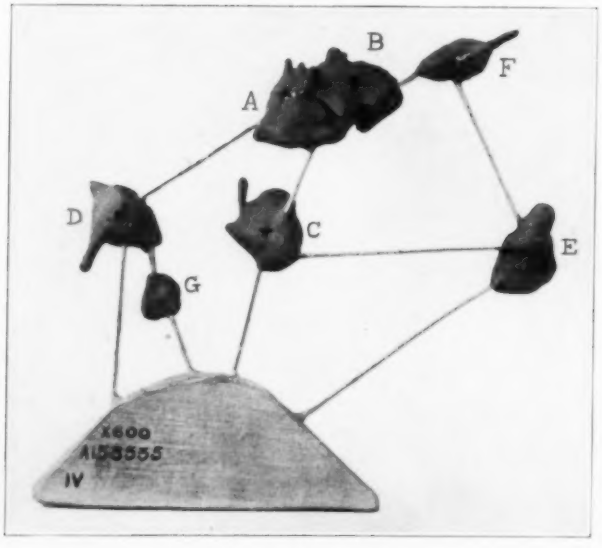


Fig. 2.

are in an advanced stage of degeneration; in the other two, F and G, they have completely disappeared.

Case II.—A-165975, Fig. 3. This reconstruction is from a group of ganglion cells in the right superior cervical sympathetic ganglion of a male 30 years of age who had had severe symptoms of exophthalmic goiter for three months. His left superior thyroid vessels had been ligated nine days and his

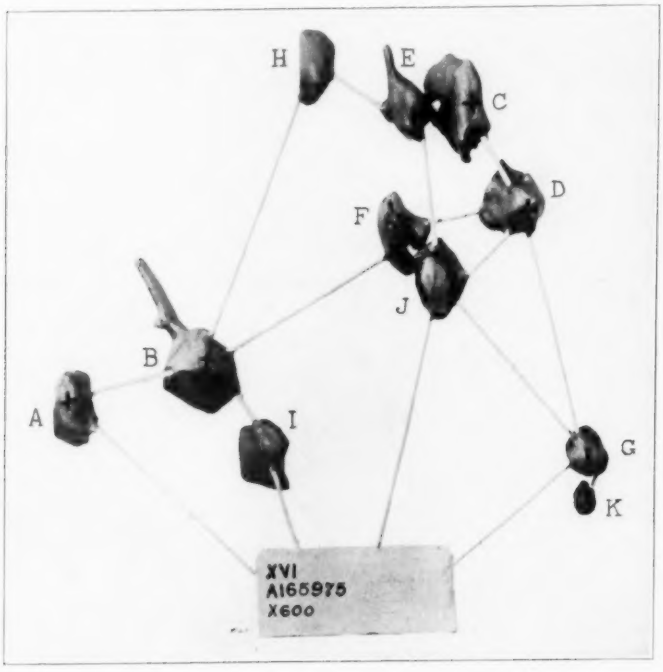
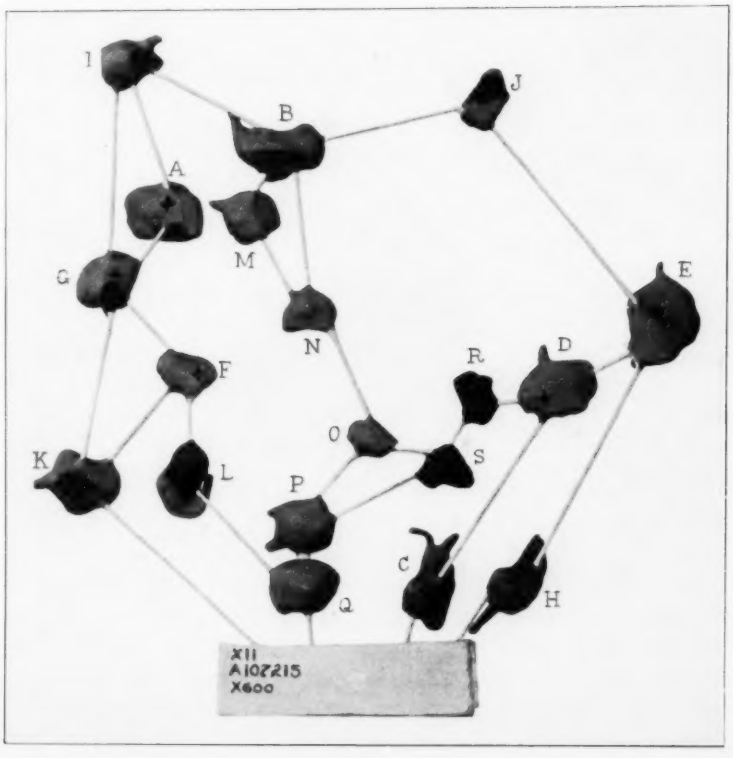

H
E
C
D
F
J
B
A
I
G
K
XVI
A165975
X600

Fig. 3.


I
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O
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L
S
P
C
H
Q
XII
A107215
X600

Fig. 4.

right superior thyroid vessels four days before his death, the immediate cause of which was a bilateral disseminated bronchopneumonia. His myocardium showed very marked fatty changes. Of the eleven cells shown, four, A, B, C and D, are apparently normal, both in their cytoplasm and nuclei. One, E, is atrophied and the nucleus is in an advanced stage of degeneration but without pigmentation in the cytoplasm. In two, F and G, there is advanced destruction of the nuclei, atrophy and advanced pigmentation. In two, H and I, there is atrophy and complete destruction of the nuclei, but no pigmentation. In one, J, there is some atrophy, advanced pigmentation and complete destruc-

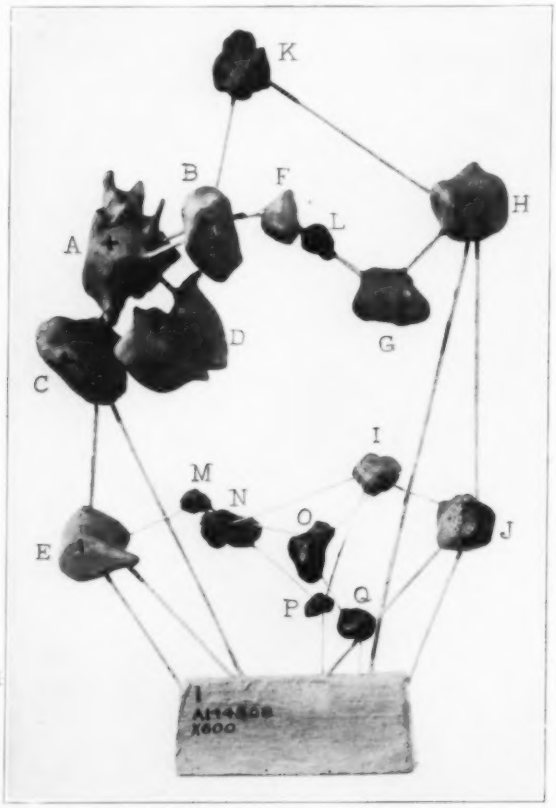

Fig. 5.

tion of the nucleus. Of one, K, only a mass of pigment about 1/8 the normal size of the cell remains.

Case III.—A-107215, Fig. 4. (Case I, Ref. 3.) This reconstruction is from a group of ganglion cells in the left superior cervical sympathetic ganglion of a female 24 years of age who had had symptoms of severe exophthalmic goiter for four months. Of the nineteen cells shown, five, A, B, C, D, and E, are apparently normal in size, character of protoplasm, and the nuclei. One other, F, may be normal, although it is quite small. Two, G and H, are heavily pigmented but show nuclei which are apparently normal. Four, I, J, K, and L are heavily pigmented and show no nuclei. Five, M, N, O, P, and Q,

are atrophic, show no pigment but are without nuclei. Two, R and S, are reduced to relatively small masses of pigment only.

Case IV.—A-144809, Fig. 5. (Case III, Ref. 4.) This reconstruction is from a group of ganglion cells of the left superior cervical sympathetic ganglion of a female 30 years of age who had had severe exophthalmic goiter for eight months. Of the seventeen cells shown, two, A and B, show apparently normal protoplasm and nuclei though they are hypertrophied. One other, C, near them is markedly hypertrophied and though its nucleus is normal it shows beginning pigmentation. Another, D, in the immediate vicinity is markedly hypertrophied, shows beginning pigmentation and its nucleus has completely disappeared. One, E, which is normal in size shows beginning degeneration of the nucleus and no pigmentation. Three others, F, G, and H, though showing no pigmentation, show complete destruction of the nucleus. Two, I and J,

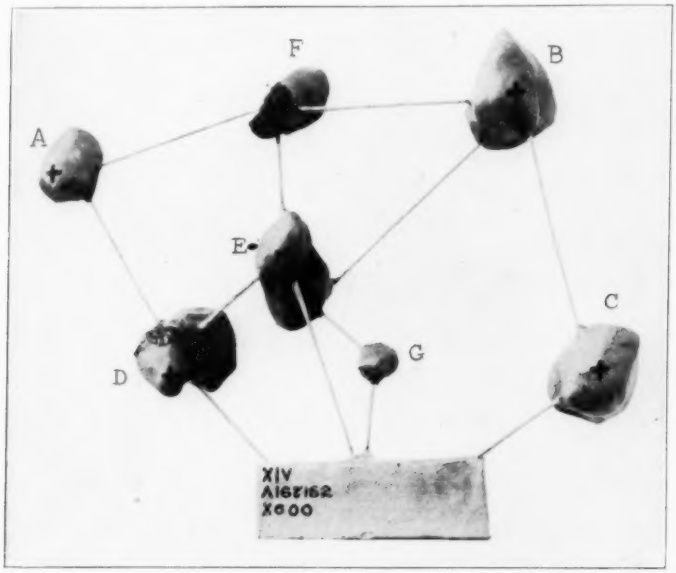

Fig. 6.

show advanced pigmentation with destruction of the nucleus, and seven, K, L, M, N, O, P, and Q, are reduced to atrophic masses of solid pigment.

Case V.—A-167162, Fig. 6. This reconstruction is from a group of ganglion cells in the right superior cervical sympathetic ganglion of a female 24 years of age who had had very severe symptoms of exophthalmic goiter for 3 months, remission of symptoms for 4 months, a severe relapse for 2 months, and then almost complete remission of all symptoms except severe exophthalmos during the last 6 months preceding operation (sympathectomy). Throughout the sections from this case hypertrophy of the ganglion cells was marked. In the group shown, one cell, A, is apparently normal in size, composition of its protoplasm, and character of its nucleus. Two, B and C, are very markedly hypertrophied, but with nuclei which show no degenerative changes. One, D, is hypertrophied and pigmented but with an apparently normal nucleus. Another, E,

is hypertrophied with an apparently normal nucleus. Another, F, is pigmented and shows no nucleus. Another, G, is atrophied, nonpigmented and without a nucleus.

Case VI.—A-129966, Fig. 7. (Case II, Ref. 3.) This reconstruction is from a group of ganglion cells in the left superior cervical sympathetic ganglion of a female 30 years of age who had had severe symptoms of exophthalmic goiter for a year. An examination of the sections from this ganglion showed in most areas a marked atrophy of the ganglion cells. The group selected for reconstruction is from an area in which the cells are hypertrophied. In the model each cell is bisected and on the cut surface are indicated the pigmenta-

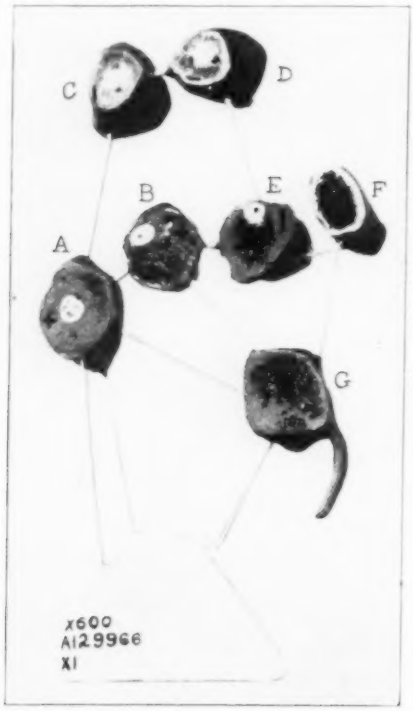

Fig. 7.

tion and appearance of nuclei; the latter is also indicated by the arbitrary signs. A photograph has been taken of the model with the loose portion of each cell removed. Of the seven cells shown, none are normal though two, A and B, show nuclei without material degeneration. In three others, C, D and E, degeneration has begun in the nuclei, and in two, F and G, the nuclei have completely disappeared. All the cells are markedly pigmented.

Case VII.—A-136418, Fig. 8. (Case IV, Ref. 4.) This reconstruction is from a group of ganglion cells in the superior cervical sympathetic ganglion of a female 25 years of age who had had moderate symptoms of exophthalmic goiter for one year and eight months, a period of exacerbation lasting three weeks and then partial relief by double ligation of the thyroid vessels fol-

lowed 4½ months later by thyroidectomy. At autopsy nine days after operation the cervical sympathetic ganglia were noticeably enlarged. Of the thirteen cells shown, two, A and B, are apparently normal. Three others, C, D, and E, show normal nuclei but are stained by diffuse pigmentation. Three others, F, G, and H, show normal nuclei, diffuse pigmentation, and in addition, masses of heavy pigmentation. One, I, shows diffuse light pigmentation and a partially degenerated nucleus. Two, J and K, show diffuse light pigmentation, masses of heavy pigmentation, and no nuclei. Two, L and M, show complete absence of nuclei.

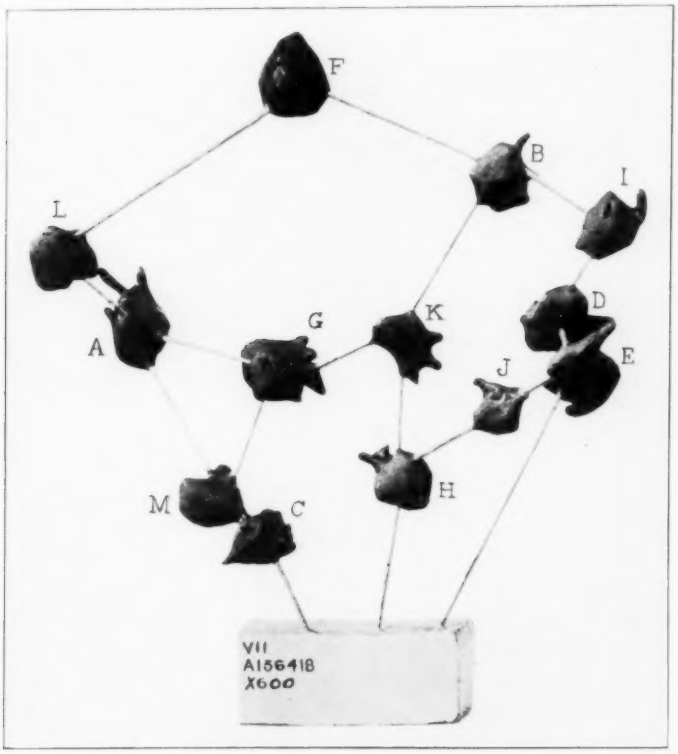

Fig. 8.

Case VIII.—A-135172, Fig. 9. (Case VII, Ref. 4.) This reconstruction is from a group of ganglion cells in the right superior cervical sympathetic ganglion of a female 39 years of age who had had moderate symptoms of exophthalmic goiter for twelve years with gradual abatement of symptoms for four years. Microscopically the total number of ganglion cells was apparently much reduced. The condition of those remaining is well represented in the reconstruction. None of the cells are normal. Nine of the ten are heavily pigmented. In the tenth, J, the nucleus is degenerated. Of the nine pigmented cells, five, A, B, C, D, and E, show quite normal nuclei. One, F, shows a partially degenerated nucleus. In one, G, the nucleus shows advanced degeneration, and two, H and I, are without nuclei.

Case IX.—A-53650, Fig. 10. (Case XV, Ref. 3.) This reconstruction is from a group of ganglion cells in the left superior cervical sympathetic ganglion of a female 21 years of age who after a year of suffering from severe symptoms of exophthalmic goiter had had double ligations of the superior thyroid vessels followed four months later by removal of the right lobe of the thyroid. Three years and eight months after the removal of her right thyroid, her left superior cervical sympathetic ganglion was removed. Examination of sections of this ganglion showed marked diminution in the number of ganglion cells. Of those which remained, few were normal. In the group of twelve shown, one only, A, is apparently normal. One, B, is normal except

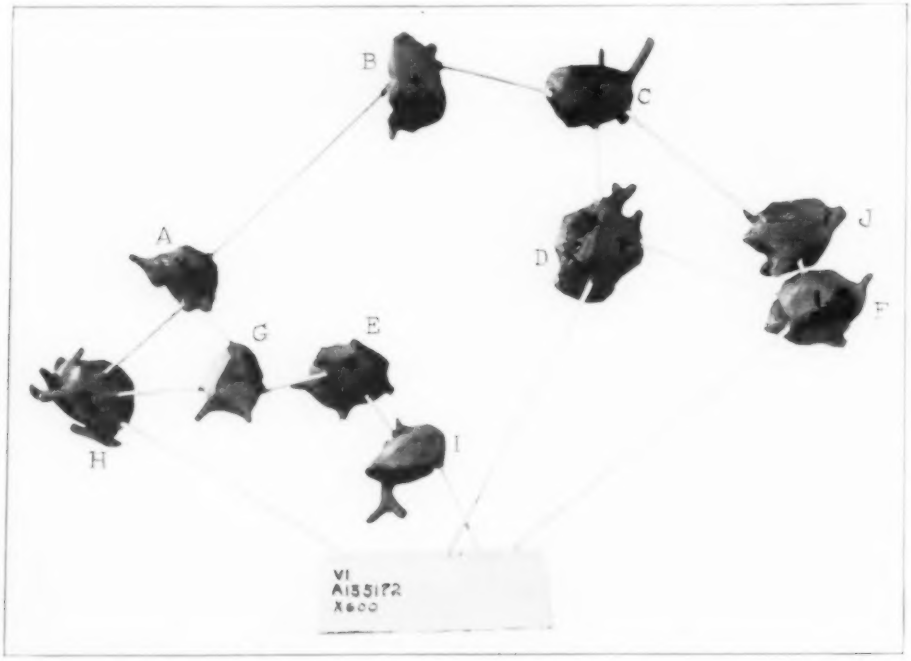

Fig. 9.

for a diffuse light pigmentation. One, C, shows intense local pigmentation but with an apparently normal nucleus. Three, D, E, and F, show similar pigmentation but with degenerated nuclei. Three, G, H, and I, show pigmentation with complete destruction of the nucleus. Two, J and K, are markedly atrophied, without nuclei and without pigmentation.

DISCUSSION.

These reconstructions of groups of ganglion cells have confirmed the impressions received from the microscopic study of series of sections of ganglia and made it possible to demonstrate their truth beyond a doubt. The material studied is all from patients so young as to preclude the possibility of senility as a factor in the changes observed in the ganglion cells. The material was all

in excellent condition when preserved. The methods of preservation, preparation, and reconstruction eliminate technical artefacts.

A study of the distribution of the cell changes in the groups illustrated shows that in every group there are cells which are apparently capable, of function, though in some instances this may be somewhat impaired in all the cells. At the same time in each group there are also cells which are apparently totally incapable of function. These two forms are in close relationship to each other. If we conceive of a distant muscle fiber or group of thyroid epithelial cells as controlled by a neuron, of which the ganglion cells of the functionating type are a part, then we must conceive of such muscle fiber or glandular epithelium as capable of being stimulated and, unless otherwise prevented, of functionating. Conversely, muscle fibers and glandular epithelial cells receiving

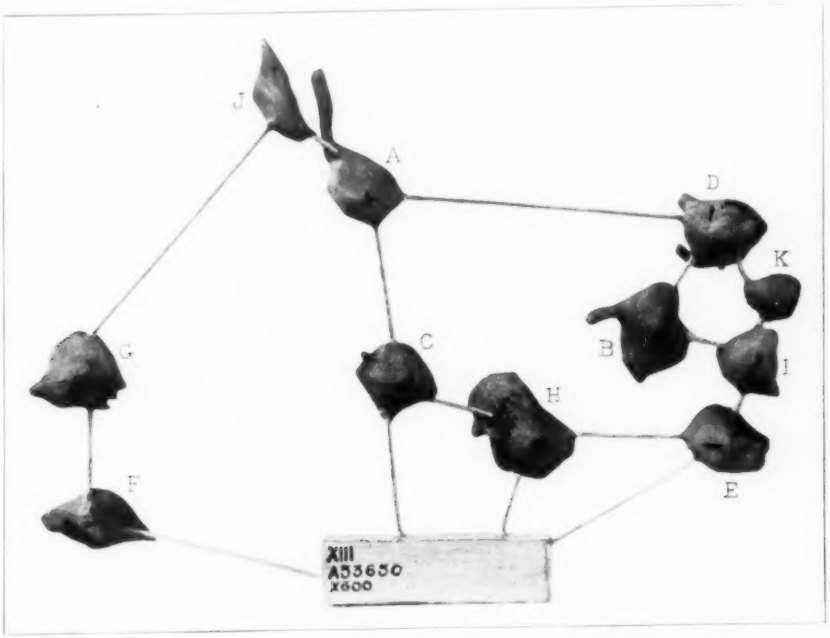

Fig. 10.

their nerve supply from neurons of which destroyed ganglion cells are a part, cannot receive their stimuli to function through such neurons. Unless another neuron vicariously assumes the function of the one in which the broken link exists, the muscle fiber or glandular epithelium must perforce go out of commission. The fact that functionating ganglion cells are in immediate proximity to nonfunctionating cells is in close harmony with the fact that in exophthalmic goiter we have muscle fibers and thyroid glandular epithelial cells in advanced stages of degeneration in immediate proximity to others of their kind which are apparently normal. That the changes in the ganglion cells may be secondary to primary changes in the muscle and glandular epithelium is rendered improbable by the fact that similar changes are not found in cervical ganglia of patients from whom a lobe of the thyroid has been totally removed

for many months. Atrophic changes in the ganglion cells from ablation of the distant organ controlled by neurons of which the ganglion cells were a part are very different from the granular degeneration seen in cases of exophthalmic goiter. Nor do the changes seen in ganglion cells of persons of advanced age at all closely resemble those herein illustrated. Indeed there is every resemblance in the changes in the cervical ganglion cells in exophthalmic goiter to the changes in the ganglion cells in the spinal cord in anterior poliomyelitis and to the changes in the cortical cells of the cerebrum in meningitis. They may best be explained on the hypothesis of a specific primary infection of the ganglion itself.

NOTE ON THE TECHNIC USED IN THE RECONSTRUCTION OF GANGLION CELLS AT HIGH MAGNIFICATIONS.

The reconstructions were made from serial sections of tissue, stained by Ramon y Cajal's 1910 silver impregnation method and cut at 5 and 10 micra. In all, eighteen* reconstructions of ganglion cells were made. Sixteen models were groups of ganglion cells reconstructed at a magnification of 600 diameters. Five of these were from human tissue removed at operation, eight from human tissue removed at autopsy, two were groups of cells from a goat, and one was of cells from a brook trout. Two models were reconstructions of single human ganglion cells at a magnification of 3,000 diameters. One of these showed a moderately degenerated cell, and the other a practically normal cell with its intracapsular processes and axone.

In making drawings for the above reconstructions at high magnifications, variations from the ordinary technic were found necessary. The principal difficulty encountered was that of tracing a single cell in serial sections. The usual method of selecting some definite landmark, such as a blood vessel, nerve process or some particular part of the ganglionic capsule which presented a comparatively uniform appearance throughout the series studied, proved successful for magnifications as high as 600 diameters. With magnifications of 3,000 diameters the cell studied covered almost the entire microscopic field, and no identification marks appearing throughout the series could be found. In order then to accurately trace a cell from section to section at this magnification, the entire series was drawn at a low magnification where definite landmarks or guides could be followed, and it was then possible to identify the different sections of a cell at much higher magnifications. When a section of a cell was located at a low magnification, it was exactly centered in the microscopic field, the higher power ocular and objective put in place, and the cell drawn.

The diameters of the normal, or nearly normal, cells were found to vary from 30 to 50 micra. Thus, in 10 micra sections, there were four or five sections to a cell, while in the 5 micra the average was from eight to ten sections. Cells showing advanced stages of degeneration were sometimes as small as 5 to 8 micra in diameter.

*Only 10 are herein shown and described. The others will be published later in relation to other studies.

The alignment and transfer of the drawings to wax plates were done with the aid of translucent paper as described by Kashtshenko[5] so that a single section of a group of cells could be placed in exact registry over the section just proximal or distal to it. On the first section of a group two lines were drawn perpendicular to each other. Several crosses were placed in rather arbitrary relation to these lines. The second section then was fitted accurately over the first section, and these lines and crosses duplicated on it. The same procedure was followed throughout the series. Thus, though there might be a variation in the position of a section of a cell in a series due to an oblique cut, or perhaps to a natural variation, it was still accurately shown by these lines and crosses.

In transferring the drawings to the wax plates, the lines and crosses were also transferred. When the wax was cut, the marks were preserved in the form of bridges and guides and, when piled serially in the usual method, wire was substituted for the wax bridges.

In coloring the models the colors used were selected to conform as nearly as possible with the color which each cell stained by the silver impregnation method. Thus, in a single group, several shades were frequently used. The relative extent and depth of staining of the pigment is indicated by dots on the surface of the models. Each cell, if marked at all, bears a +, 1, or – sign, indicating

\+ = Normal nucleus.

1 = Earlier stages of degeneration of the nucleus.

– = Advanced stages of degeneration of the nucleus.

No mark = No nucleus found in any of serial sections of the cell.

The wax plates were made for us in the Anatomical Department of the University of Minnesota through the kindness of Prof. Thos. G. Lee.

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PIPERAZIN AND OTHER ORGANIC URATE SOLVENTS*

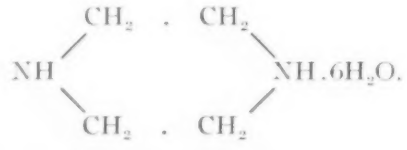
By Paul J. Hanzlik, M.D., Cleveland, Ohio.

IN a previous paper on hexamethylenamine (Hanzlik, 1916) a review of the literature revealed the practically negligible position of this drug among the so-called urate solvents, particularly when contrasted with such well known and tried alkalies as the bicarbonate and citrate of sodium. Special urate solvent properties have been ascribed to other agents. Among the best known and widely exploited, of these is piperazin. However, our knowledge of the behavior of uric acid and urates in the body and its fluids makes it difficult to understand why any special virtues should be ascribed to this product.

It is the object of this paper to examine the literature on piperazin and other urate solvents and to ascertain what, if any, scientific data exist to support the claims that are made. A proper appreciation of the chemical properties and the behavior of uric acid and the urates in the body is necessary in order to judge the data. For this the previous paper may be consulted. The complexity of the chemical behavior of the urates is further illustrated in recent contributions by Lambling and Debaussy (1914) and Haskins (1916). These emphasize the paradoxical behavior of the solvent power of urine itself for uric acid, and other properties, rendering positive deductions extremely difficult. It may be further stated that positive and optimistic statements regarding the therapeutic efficiency of the class of substances called urate solvents should be generally regarded as premature and unfounded, particularly if it is remembered that the clinical conditions for which these are frequently recommended are still more obscure. Bearing these uncertainties in mind, we may now proceed to examine the possibilities offered by piperazin as a urate solvent.

I. Addition of Piperazin to Pure Urate.

Piperazin is a synthetic organic base obtained by the condensation of two ethylene with two amino groups. It forms soluble salts with uric and other acids. Its structural formula is



Solubility of Piperazin Urate.—Piperazin dissolves uric acid even in the cold, 1 part of the salt, piperazin urate, being soluble in 50 parts of water at 17° (Mayer and Schmidt, 1890). According to Mathews (1915) the piperazin salt of uric acid is much more soluble than the alkaline salts, the solubility

*From the Pharmacological Laboratory, Western Reserve University, Cleveland. This review was prepared at the request of the Therapeutic Research Committee of the Council of Pharmacy and Chemistry of the American Medical Association.

being about 1 in 50 parts of water at 17°. Biesenthal and Schmidt (1891) give the solubility of various urates in water as follows: Piperazin urate 1:50; acid sodium urate 1:1200 at 15°; lithium urate 1:367 at 20°. Vicario (1902) reports that 1 part of piperazin urate is soluble in 45 parts of water at 18°, in 44 parts at 37°; 1 part of acid sodium urate in 1,136 at 18°, and in 581 parts at 37°. This is less than that reported by Vicario for sodium urate which was found to be 35 parts at 37°; somewhat higher, 59 parts, at 18°. 1 part of potassium acid urate was soluble in 666 at 18°, and 345 at 37°. Helbing and Passmore (1894) claim that piperazin can form an acid salt with uric acid, but that this never occurs in therapeutic practice. They claim further that neutral piperazin urate is the normal urate produced by the solvent action of piperazin on uric acid. It is said to be extremely soluble, 1 part piperazin urate dissolving in 50 parts water at 17°, in 40 parts at 38°. These data agree favorably with those reported by others as pointed out above. In attempting to compare the solubility of uric acid in piperazin in low or therapeutic concentrations, Helbing and Passmore worked with percentages that are altogether too high. They state that the concentration of 0.025% would approximately represent the percentage of piperazin in the blood after a dose of 15 grains (about 1 gm.). However, it is not correct to assume the distribution of the drug to be limited to the blood only. The tissues as a whole should be considered. The weight of the individual is not stated, but assuming it to be an adult of about 70 kilos, the concentration in the tissues, as a matter of fact, would be about 0.001%, and 0.002% for a 50 kilo individual.

Comparison With Lithium and Effect of Neutral Salts.—In test-tube experiments, according to Cushny (1910) and Schmiedeberg (1909), the solubility of uric acid in piperazin is greater than that of lithium and borax. Heinz (1907) states this to be about twelve times that of lithium carbonate; Helbing and Passmore (1894) about seven times. This is denied by Van der Klip (1892) who found the solvent power of piperazin (concentration unknown) to be less than that of lithium carbonate between 16° and 36°. Plugge (1895) states that it is only in high concentrations that piperazin is a better uric acid solvent than lithium. In dilute solutions it is less so. Ortowski (1900) found that piperazin in aqueous solution at 37.5° possessed less solvent power for uric acid than lysidine but acted somewhat more favorably than sodium bicarbonate.

In the presence of even small quantities of sodium chloride (less than 1%) this solubility is lessened, hence in urine the solvent power of piperazin is almost completely lost. Morhorst (1896) states that the addition of sodium chloride, sodium sulfate and other neutral salts to a piperazin solution of uric acid causes precipitation of urate from the piperazin urate. According to Penzoldt (1900) the solvent power of aqueous solutions of piperazin is lessened by the addition of urine. He found that a uric acid stone placed in a 1% solution of piperazin and incubated for 24 hours was dissolved along the edges only. Nicolaier (1899) thought that piperazin dissolved uric acid and urates less readily than hexamethylenamine. On the other hand, Stevens and May (1911) found that piperazin was a better solvent than hexamethylenamine.

It may be concluded that piperazin forms a salt with uric acid called piperazin urate, whose solubility is about 1 in 50 parts of water, and that this is diminished by the addition of urine and weak concentrations of neutral salts. Lithium apparently is a better solvent for uric acid *in vitro* than piperazin in low concentrations.

2. ADDITION OF PIPERAZIN TO URATE CALCULI.

Casper (1897) observed that as solvents for calculi piperazin, lysidine and hexamethylenamine were no more effective than urine or water alone, but glycerin was superior. Biesenthal and Schmidt (1891) observed that 1% piperazin dissolved a urate stone better than lithium carbonate, sodium carbonate, and borax of the same strength. Gordon (1894) treated natural vesical calculi with piperazin, borax, sodium bicarbonate, lithium citrate and potassium citrate. One per cent piperazin was found to possess considerable solvent power if the contact was long enough. The calculi were softened, rendered mushy and it was conceived that in the body they would be somewhat more easily "absorbed." When 50 mgm. of a powdered stone consisting of 59.19% uric acid was placed into 1% piperazin for 24 hours at 39°, 48 mgm. were dissolved while the other solvents under the same conditions dissolved only 25 to 35 mgm. This led to the conclusion that the solvent power of piperazin under like conditions is greater than that of borax, lithium citrate, sodium bicarbonate or potassium citrate. On the other hand, Van der Klip (1892) found that uric acid calculi are not dissolved by piperazin as readily as by lithium carbonate.

Ebstein and Sprague (1891) used piperazin as a solvent in the course of analytic procedure and found that gouty tophi consisting of urate can be dissolved by 1:1000 piperazin *in vitro*. Finzelberg (cit. Helbing and Passmore, 1894) is said to have made experiments demonstrating the solvent power of piperazin for different kinds of stone, and from this he suggested the use of the drug in the treatment of arteriosclerosis, "compound" sclerosis and atheromatous changes of the aorta.

It may be concluded that piperazin, in rather high concentration, possesses some power to dissolve calculi, but the extent of this may be regarded in some cases limited and doubtful, due in part, no doubt, to the uncertain and variable composition of calculi.

3. SOLUBILITY OF URIC ACID AND URATE IN SERUM CONTAINING PIPERAZIN.

The existing scientific data, though limited, indicate this to be of no practical importance.

Sir W. Roberts (Croonian Lectures, 1892) stated that the addition of 0.1 to 0.2% piperazin to blood serum or synovial fluid had no effect in increasing the solvent power of these media on sodium biurate, nor did it retard the precipitation of uric acid from serum and synovial fluid.

Bohland (1894) found that 50 c.c. of serum (horse and calf) containing 1% piperazin dissolved about 0.1 gm. uric acid at ordinary room temperature, that is, about 0.2%. From this solution (on standing), or when serum is added

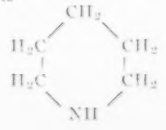
to an aqueous solution of piperazin, a flocculent precipitate is formed consisting chiefly of biurate. The solubility of potassium acid urate in 1% piperazin was found to be the same as for uric acid. Tunicliffe and Rosenheim (1898) found the solubility of sodium biurate in beef serum to be 1:31,000; other solvents in order of increasing efficiency being lysidine 1:25,000; hexamethylenamine 1:14,000; and piperidin* 1:12,000. The solubility in serum alone was found to be 1:60,000, which, if given the value of 1, would give piperazin a value of 1.9. The true reaction of the serum in all these experiments is not indicated, and as it might conceivably become strongly alkaline (by decomposition) the value of the results is considerably minimized.

4. SOLVENT ACTION OF PIPERAZIN URINE ON ADDED URIC ACID.

The solubility of uric acid in piperazin urine is much less than in aqueous solutions and it is markedly influenced by dilution and the reaction. Unfortunately the effects of dilution and reaction have been overlooked by a majority of the earlier observers.

Helbing and Passmore (1894) found that urine interferes with the urate solvent action of piperazin. They observed that 100 c.c. of 1% piperazin urine dissolved only from 0.0065 to 0.03 gm. of uric acid in 72 hours; 100 c.c. of 0.1% piperazin urine dissolved from 0.0004 to 0.0017 gm. uric acid in 72 hours. Goodbody (1896) observed that the addition of 0.1 gm. piperazin to 220 c.c. urine, 0.2 gm. in another, which regularly deposited urate, dissolved the urate to the extent of 0.01%. The average uric acid content of 5 urines before the addition of piperazin was 0.058%, and this was increased to 0.067% by the addition of 0.2 gm. of the drug. The addition of piperazin (0.085 to 0.68%) to urine (100 c.c.) containing added uric acid caused variable quantities (28.12 to 233.32 mgm. respectively) of the latter to go into solution (Haskins, 1916). This was also true of dilute and less dilute urines after the administration of the drug and whether the reaction was truly acid or alkaline. Dilute urines without the drug but possessing the same reactions frequently dissolved more uric acid than when they contained piperazin. Generally, alkaline urines dissolved more uric acid, but it is also true that Haskins found considerable uric acid dissolved in a few acid urines. After the administration of 1 to 2.5 gm. daily to 2 individuals during the course of 3 days, Heubach (1891-2) observed that the piperazin urine would not dissolve any added uric acid even at higher temperatures and with prolonged action. Meisels claims that 70 per cent of added uric acid (presumably to urine) was dissolved at room temperature. However, complete data are not cited in the report which was available. Mendelsohn (1892) could demonstrate no solvent action on calculi or uric acid in piperazin urines and concluded from this that no better results

*Piperidin is a rather active substance pharmacologically, causing a rise of blood pressure in cold blooded animals, cardiac inhibition with large doses, and a curare-like action on motor nerve endings. According to Oesterle (1909) the formula is



could be hoped for from injections into the bladder, because such solutions can be retained for 2 to 3 hours only, and the solvent effect would decrease with the advent of urine, rendering the solvent action of piperazin practically useless. Penzoldt (1900) states the uric acid solvent properties of aqueous solutions of piperazin are lessened by the addition of urine. Tunicliffe and Rosenheim (1898) found that 100 c.c. of a 0.2% piperazin urine dissolved 0.058 gm. or 11.6% of 0.5 gm. of added uric acid; 100 c.c. of 0.1% piperazin urine dissolved 0.0415 gm. or about 8.3%. Urine alone dissolved extra uric acid, and if the value of 1 is assigned to urine, the value for 0.2% piperazin would be about 13.5, for 0.1% it would be 5.7. Piperidin and lysidine were found to be more effective, hexamethylenamine less efficient. Weiss (1900) states that urates of piperazin and lysidine are soluble in water, but not in urine, an objection that cannot be held against urosin (to be considered later).

5. EFFECT ON URATE DEPOSITS.

Experimental Deposits in Birds.—Deposits in the various organs of birds produced by foreign substances have been regarded by some investigators as the clinical equivalent of urate deposits in various disease conditions in human individuals, and gouty tophi. It is apparent that the conclusions drawn from such uncertain analogies furnish a very insecure basis for the therapeutic efficiency of the so-called urate solvents in gout and similar conditions. Nevertheless, we may briefly allude to the effects of piperazin in this interesting avian condition.

Fawcett (1894) observed that deposits produced in pigeons by gradual injections of chromate disappeared after the injection of 0.001 to 0.0005 gm. piperazin. The kidneys were found to be swollen, pale or mottled, and Fawcett suggests that as a result of the piperazin injections the outlet for uric acid was blocked and the uric acid "deposited" in the tissues. Presumably retention of uric acid rather than actual deposits was intended. Practically the same was observed by Meisels (1893), who found that not only could piperazin prevent the formation of deposits but also remove those already formed. Whereas control animals showed a parenchymatous nephritis and uric acid concrements in the tubules, those treated with piperazin were free from these. Lithium carbonate and sodium bicarbonate were found to be without any influence on urate deposits in birds. Waucomont (1912) produced experimental gout in chickens by the feeding of horse flesh, and observed the effects of various urate solvents on this. It was found that piperazin, lycetol, sidonal and potassium iodide produced no influence on the excretion of uric acid, and most of these agents also did not influence the course of the clinical condition. The disappearance of joint swellings, deposits and symptoms of gout in an eight year old parrot following the administration of piperazin (0.08 gm. daily) is reported by Zimmermann (1901). However, since the patient received bicarbonate internally, and salicylated collodion locally together with the piperazin treatment, it cannot be concluded which, if any, of the beneficial effects were due to piperazin alone. Biesenthal (1893) claims to have confirmed the work of Meisels (1893), and thereby procured support for the therapeutic claims made

for the drug in "uric acid diathesis." Both chickens and pigeons were used. About 7% of the animals injected with chromate failed to respond with demonstrable urate deposits. Eighty per cent (16) of the chickens and 82% (14) of the pigeons treated with piperazin showed no deposits. However, since a considerable number of animals fail to give evidence of deposits with repeated injections of chromate, a large element of uncertainty must exist in this form of experimentation, likewise in the conclusions drawn therefrom. Proportionately for human individuals, the doses used by Biesenthal were very large, a total dosage of 27 gms. having been administered. Lithium carbonate, sodium phosphate and borax are reported by Biesenthal not to have influenced the deposits.

Deposits in Gout and Other Conditions.—According to Meyer and Gottlieb (1914) the view that piperazin and lysidine cause removal of retained uric acid in the tissues has been found to be erroneous. Mordhorst (1892) observed that piperazin would be a good solvent for urates, but a 1% solution, which is effective, is inconceivable in the body, the concentration in blood being about 0.0125%. A disappearance of uric acid crystals in standing urine was noticeable, but the same followed more completely with the use of mineral waters. Mordhorst points out that the excretion of piperazin after internal administration, its destruction in part, and the doubtful affinity displayed by piperazin for uric acid being greater than that of the alkaline salts of the blood are important additional reasons why such agents as piperazin and lysidine cannot act favorably on urate deposits in the living organism. In a later communication, Mordhorst (1896) emphasizes the absurdity of expecting the alleged solvent effects of piperazin. He states that piperazin cannot act in the living organism because of the homeopathic concentration of the drug in the body, about 1:54,000, and it must be remembered that a ½% solution dissolves uric acid very little, ¼% still less and ⅛% not at all. "It is therefore not understandable how anyone can earnestly believe that a solution of this salt, 1:54,000, can have even the slightest uric acid solvent action." Yeo (1909) quotes Sir Roberts to the effect that both piperazin and lithium cannot prevent the formation of uratic deposits.

6. EFFECT OF THE ADMINISTRATION OF PIPERAZIN ON URIC ACID AND URATES.

According to Haskins (1916), who has furnished the best scientific evidence on this subject, piperazin in small doses does not affect the excretion of uric acid in urine. Using proper controls and carefully observing the reaction of the urine (hydrogen-ion concentration), Haskins found that when piperazin is administered in very large doses only (extra therapeutic) there is some increase in the excretion of uric acid. However, this was more effectively produced by the administration of ordinary alkalies such as citrate and bicarbonate of sodium. The use of large doses of piperazin according to some clinical reports (to be referred to later more fully), is perhaps harmful, and, therefore, not justified, particularly in view of the fact that the same object may be attained by the use of well tried and relatively harmless alkalies. The work of

Haskins is confirmatory of certain of the older observers, although it must be admitted that there is an element of uncertainty in their work owing to the lack of proper dietary and other controls, the failure to realize the importance of the reaction of urine, the influence of diuresis and the variable solvent power of urine itself. An exception to the older work is that of D. D. Stewart, and it agrees essentially with that of Haskins.

D. D. Stewart (1893) showed quite conclusively that medium-sized doses of piperazin used over long periods are without effect on uric acid excretion. This observer carefully studied the volume of urine, specific gravity, acidity, urea and uric acid excretion daily before and after the administration of the drug for several days in 3 cases of renal stone, using also proper fluid intake and, apparently, dietary controls. The dosage of piperazin was about 24 grains (1.5 gm.) daily for 14 days in each case. Under these conditions there was no increase in uric acid elimination demonstrable and attributable to the drug, also no increase in urea excretion. Later observations by Stewart (1894) with even larger doses of the drug, 70 grains (nearly 5 gm.), daily, confirmed his previous results. That is, the excretion of uric acid, urea and chloride remained uninfluenced.

The following abstracts are cited against piperazin as a urate solvent: According to S. Fraenkel (1912) objective experiments indicate that the uric acid solvents, such as piperazin and others pertaining to its class, are worthless and when effects are seen, these are produced more by other conditions. Percy May (1911) is of a similar opinion; namely, that while some benefit may be derived from the administration of the piperazin class of urate remedies, this is not due to their solvent action on the uric acid. The employment of these bases as uric acid solvents is fallacious because there is always sufficient sodium present in the body to form the sparingly soluble sodium urate. Further, owing to the detrimental effects of small quantities of sodium chloride on the solvent power of piperazin, and the fact that it is to a large extent destroyed in the body, leaving only a small quantity unchanged in the urine, the uric acid solvent action of the drug on internal administration seems very problematic (Heinz 1907). According to Cushny (1910) the urine of patients receiving piperazin has no more solvent action on uric acid than urine itself; and whatever piperazin escapes into the urine is in combination with the stronger acids and not uric acid. Hare (1905) states that repeated clinical observation has shown that the administration of the drug causes an increase in the amount of urea in the urine with decrease in uric acid indicating that under its influence oxidation is more complete. He gives no data. Various conditions in which piperazin is used and recommended are, in Hare's experience, not benefited by the administration of the drug. Likewise Penzoldt (1900) claims he could recognize no influence by piperazin medication on the decrease of uric acid excretion. Poullson (1912) doubts, (for well known reasons, previously mentioned), whether piperazin has ability to dissolve uric acid in the organism.

In a case of leukemia which showed increased uric acid excretion and urate deposits in urine, Bohland (1894) found that during piperazin treatment, as well as with potassium bicarbonate, and when no urate solvent was administered,

the excretion remained the same. In spite of large doses, piperazin did not affect the deposits but these were removed by potassium bicarbonate. Ebstein and Sprague (1891) administered 14 grams of piperazin within 7 consecutive days and carefully observed the quantity of uric acid excreted together with proper control of dietary and fluid intake. There was only a slight, and practically negligible increase in uric acid excretion, the urine output during this time being variable. Fauvel (1908) found that small doses of piperazin (1 gm. daily) diminished the excretion of endogenous uric acid, the diet during this time being purin free, but when the dosage was increased (2 to 4 gm. daily) the excretion of uric acid was increased, but not above the quantity before piperazin was ingested.

Ortner (1908) claims that piperazin seems in some cases to be effective as a therapeutic agent, its action being explained by its power to dissolve uric acid. However, Ortner emphasizes that he never prescribes piperazin alone, but with a bottle of Seltzer, Preblau or soda water, to which, no doubt, may be ascribed a considerable, if not the greater, share of the supposed solvent action. Using the colorimetric method of Folin, Robertson (1914) observed that piperazin as well as a number of other substances (pituitary, saline, $Ba\,Cl_2$, caffeine and $Na_2\,S\,O_4$) produced in hens no changes in uric acid excretion sufficiently independent of urine flow to suggest any specific effect of the agents used.

The following is a summary of reports favorable to piperazin, though scientifically not acceptable:

Abl (1913) claims that piperazin produced an increase in the urinary excretion of uric acid, and the same is reported by Abl for a number of diverse agents such as mustard, arsenic, colchicine, thorium X, sulfur, choline, chloral hydrate, neurine and strontium! The mechanism of action, Abl believes, is located in the intestine. However, it seems quite probable that diuresis at least in part (contrary to the claim of the author) and other factors, such as disease, destruction, circulatory changes, etc., were responsible for the results reported by Abl. Attaix (1896) made the claim that the quantity of uric acid and urates is augmented proportionately to the urea. This and other claims of this author are not supported by any discoverable scientific data. The effect of piperazidin on the excretion of uric acid was studied by Bardet (1891), but with no urinary or dietary controls, rendering it impossible to draw any conclusions from the work. Goodbody (1896) administered piperazin in 1 gm. daily doses for 9 days, and 2 gm. daily during the next 5 days, maintaining the diet and fluid intake constant. Under these conditions uric acid excretion increased from 0.31 to 0.34 gm. on the 1 gm. dosage, and eventually increased to 0.37 gm. with the 2 gm. dosage. Goodbody concluded that administration of piperazin increases the elimination of uric acid, not by increased formation, but by rendering the blood more capable of removing it from the tissues by increasing its solvent power. However, it must be urged that these differences are small and within ordinary variations, as indicated by Goodbody's own results before the administration of the drug. Finally, granted that piperazin

produced this increase in the excretion of uric acid, it is so small and the dosage so large, and the duration of administration so long that it would be practically valueless, uneconomical and undesirable.

7. EFFECT ON DIURESIS.

There are many statements in the literature to the effect that piperazin can favorably influence diuresis, but the scientific evidences for this are deficient. Attaix (1896) makes the statement that piperazin lessens the density of urine and acts as a powerful diuretic. However, in view of the fact that only imperfect data are cited in connection with a single observation of his own, Attaix's conclusion is unjustified. The more careful observations of Bohland (1894) showed that piperazin did not change the quantity of urine voided in 24 hours. Ebstein and Sprague (1891) also found that while the urine output during administration of piperazin was variable, there was no marked change from diuresis before piperazin. Fraenkel (1912) referring to the general group of urate solvents, including piperazin, states that these agents possess chiefly a diuretic action, and dilution of urine facilitates excretion of uric acid. This statement, however, is unsupported by any data. Goodbody (1896) administered piperazin (1 to 2 gm. daily) for several days (14) to an individual whose urine exhibited deposits of uric acid gravel regularly (using proper dietary and fluid intake controls) and found that 1 gm. of piperazin increased the volume of urine from 1103 c.c. to 1476 c.c., and 2 gm. caused a further increase to 1680 c.c. A closer inspection of Goodbody's tables reveals the fact that diuresis before administration of the drug was variable, and on certain days before treatment with piperazin the values are as great as those during piperazin periods. It is hardly permissible, therefore, to ascribe any great importance to these results, particularly since the loss of water by other channels (sweat and the intestine) have not been considered. Heubach (1891-92) administered 2.5, 1 and 2 gm. piperazin on the first, second, and third days, respectively, to two different individuals and observed that only a slight increase in urine output occurred with no diminution in specific gravity. Kobert (1897) states that all of the following are diuretic in doses of 1 to 2 gm. per day; piperazin, lycetol, lysidine and hexamethylenamine, and that they may act in part by removal of water; but the evidence for this is lacking. D. D. Stewart, (1893) administered 18 to 30 grains (1.1 to 2 gm.) daily of piperazin over long periods of time (14 days) consecutively in 3 cases of renal stone and observed an increase in urine volume in one case which could be explained by a hydronephrosis present that disappeared following an operation for removal of the stone. In a later communication, D. D. Stewart (1894) claims that two different preparations of piperazin used had invariably a diuretic influence. The elimination of urea and chloride at the same time remained unaltered. Wittzack (1893) also claims that piperazin (using about 10 gm. per day) caused an increase in diuresis. However, it is not clear whether the fluid intake was controlled. Umpfenbach (1891) is reported to have observed a favorable influence on the quantity of urine excreted, and on the nerves and muscle of the bladder.

8. EFFECT ON THE REACTION OF URINE.

The scientific data on this are conflicting, although most clinicians seem to be of the opinion that the reaction is unchanged. Aside from the observations of Haskins (1916) there are no data in the literature, so far as I know, regarding the true reaction (i.e., hydrogen-ion concentration) of urine as influenced by piperazin. Haskins found that the direct addition of piperazin or lysidine to acid urines lowers the hydrogen-ion concentration (from 5 to 7.4 with a piperazin concentration of 0.68%), i.e., the reaction was alkaline. However, after administration, the reaction of urine was uninfluenced and frequently remained acid. The reactions referred to in the following papers are presumably in many cases intended to convey changes with litmus, in others, by titration. Owing to these uncertainties, the value of the abstracts is considerably diminished. Nevertheless, it seemed worth while to refer to them.

Biesenthal (1892), citing the advantages of piperazin over ordinary alkalies and waters, states that after prolonged administration of piperazin the urine remains acid, but he gives no scientific data. Bohland (1894) claims that the administration of piperazin in a case of leukemia slightly lowered the acidity of urine. Goodbody (1896) made observations as follows: The addition of 0.1 gm. piperazin to 220 c.c. of urine from a patient suffering with uric acid gravel, and 0.2 gm. to the same volume of urine from another patient whose urine regularly deposited urate, increased the acidity from 0.41% to 0.44% (NaOH) in 24 hours and 0.39% to 0.40% in 36 hours, respectively. In 5 cases the acidity of the urine was reduced from an average of 0.39% to 0.38% by the administration of 0.2 gm. piperazin. These differences are so small as to be practically negligible. Further observations by Goodbody on the effect of prolonged administration of piperazin in doses ranging from 1 to 2 gm. per day gave the following results: The average during normal days was 0.46% NaOH, and this fell to 0.36% on 1 gm. piperazin daily; 0.2 gm. piperazin daily caused a further fall to 0.30%. The conclusion reached was that piperazin has the power to diminish the acidity of urine. It must be pointed out, however, that this does not necessarily mean there was a reduction in the true reaction of the urine. Fauvel (1908) found that the reaction of urine from individuals on a purine free diet was unchanged by small (1 gm.) or larger (2 to 4 gm.) daily dose of piperazin. The administration of 2.5, 1 and 2 gm. of the drug on the first, second, and third days, respectively, by Heubach (1891-92) had no influence on the reaction of the urine, which remained acid. In the experience of Mordhorst (1892) piperazin causes only a small reduction in urinary acidity. In his observations, D. D. Stewart (1893, 1894) found that the acidity of urine was not appreciably affected by the administration of piperazin. On the other hand, Wittzack (1893) claims the acidity of urine is lowered, the urine, however, never becoming neutral or alkaline. It is not clear whether the influence of dietary in Wittzack's work was excluded or not.

9. EFFECT OF THE ADMINISTRATION OF PIPERAZIN ON CALCULI.

This feature of piperazin therapy has undoubtedly been exaggerated. The statements and opinions held regarding the favorable influence that piperazin treatment is alleged to possess on the removal and solution of calculi are unsupported by a single iota of scientific evidence. For instance, the claim of Biesenthal (1892) for the superiority of piperazin over alkaline mineral waters as a preventive of stone formation is made without foundation of fact. He also makes the surprising claim that alkaline mineral waters lead to stone formation because of phosphate precipitation. Cushny (1910) observes that piperazin has not been shown to be of any value in the treatment of calculus. Referring to its use as a preventive of the formation of renal and vesical calculi and other conditions, Hare (1905) states that he has failed to obtain any results from the use of this drug in practice. Fawcett (1894) made observations as follows: An individual was given 15 grains (about 1 gm.) piperazin daily for 2 weeks. The 24-hour specimens of urine (preserved with choloform) were collected and allowed to drip over a stone for the next 24 hours kept at body temperature. Two such experiments are reported. In one experiment the stone weighed 2.4 gm. before the experiment and 2.404 gm. at the end of the first week during treatment. The same stone in the second experiment weighed 2.4435 gm. before and 2.6155 gm. at the end of the second week. The stone contained 78.5% uric acid by analysis. The same individual's urine was again collected for 14 days, piperazin (1:1000) added to it and a portion of the same stone used in the previous experiments was added to it and another portion to water containing 1:1000 piperazin. No solvent action was observed by piperazinized urine, but complete solution took place in the water. Fawcett's simple though ingenious experiments demonstrate clearly the inefficiency of piperazinized urines, obtained either by administration, or by addition of the drug directly, to dissolve urate stone.

Maramaldi (1897) reports rather optimistically that piperazin has the power to give specific symptomatic relief in renal colic due to calculus, because, as he puts it, "the patient claimed to feel like a new born man" after 1 gm. piperazin per day. Morphine and other measures had been previously used, however, without effect. No objective evidence is offered. From experiments on pigeons, in whom it is claimed experimental urate deposits were successfully prevented and removed by the administration of piperazin, Meisels (1893) declares piperazin can easily dissolve uric acid calculi in dilute solutions, being superior in this respect to sodium borate and phosphate, and that the results with the drug clinically are gratifying. No clinical data are furnished by Meisels. Beneficial symptomatic relief in individuals suffering with calculi is claimed by D. D. Stewart (1894) whose work with the urate solvents is more critical than that of his contemporaries. However, Stewart makes it plain that the beneficial action cannot be explained by uric acid excretion and prefers to leave the mechanism of action unexplained.

The observations of Mendelsohn (1892) cast doubt on the alleged solvent action of piperazin for calculi. Mendelsohn found that while piperazin in water

dissolves uric acid calculi, no solution either of stones or uric acid takes place in piperazinized urine. He explains also that no better results can be hoped for from injections of solutions of piperazin into the bladder because they can be retained for 2 to 3 hours only and the solvent effect would decrease with the advent of urine, rendering the solvent power of piperazin practically useless, all of which clearly emphasizes the fact that when piperazin is used under conditions of the body no beneficial effect, or solvent action of the drug, is demonstrable. Mordhorst (1896), whose work has been cited in another place, also clearly explained why no beneficial therapeutic action may be expected from the so-called urate solvents. Penzoldt (1900) concurs in this view, also Poullsson (1912). H. C. Wood (1902) is of the opinion that while piperazin may be of service as a solvent of uric acid gravel, it will not dissolve a ready formed calculus in the bladder.

10. EFFECT OF PIPERAZIN IN GOUT.

The uncertain role that uric acid plays in the etiology and symptomatology of gout has not prevented certain clinicians from frequently recommending the so-called urate solvents as beneficial therapeutic agents in this condition. In view of the etiologic uncertainty, the use of such agents is certainly irrational. That the value of so-called urate solvents in gout may be considered negligible is amply confirmed by the reports in the literature which are conspicuous for lack of scientific evidence; judgment being further impaired because of the influences of other attending circumstances, various unknown factors, and allied medication. The following abstracts, therefore, possess only the value that may be attached to opinion unsupported by scientific evidence.

Heinz (1907) states that piperazin has been administered very much in gout and "uric acid diathesis" without promising results. Penzoldt (1900) agrees with this. Because, as Kobert (1897) supposes, the so-called urate solvents act as diuretics, it is suggested that they act in gout by removal of water. However, Kobert's supposition regarding diuresis is not borne out by the facts. D. D. Stewart (1894) thinks that piperazin gives relief in gouty attacks. He is not clear as to how this is brought about, but he agrees that it certainly cannot be explained by any influence on the excretion of uric acid. Zimmermann (1901) reports gout in a parrot as having been permanently benefited by the administration of piperazin. However, the bird also received sodium bicarbonate internally, and salicylated collodion locally, rendering it, therefore, rather difficult to ascribe the beneficial effects observed to any one particular agent. Attaix (1896) reports a case of gout, which had previously been treated with colchicum and salicylate, but without response. The attacks, it is claimed, were prevented by piperazin. Biesenthal and Schmidt (1892) cite 5 cases reported by Bardet who is said to have demonstrated an increase of uric acid excretion in gout, but neither the data nor the conditions under which these were obtained is mentioned.

In contrast to all this may be cited the paper of Fawcett (1894) as the only piece of scientific evidence available. Using the Hopkins quantitative method for uric acid, and suitable controls, Fawcett found that piperazin ex-

erted no effect on the excretion of this metabolite in gout, or on the relief of the symptoms. He concluded that piperazin is not as valuable as certain drugs already recognized for the treatment of this condition.

11. UNDESIRABLE ACTIONS OF PIPERAZIN.

Several reports in the literature indicate that the administration of piperazin may be attended with or followed by albuminuria, urticaria and other undesirable objective and subjective symptoms. Albuminuria due to piperazin has been claimed by Rörig (1893). Rörig reported repeated albuminuria in an individual who had had nephritis, but did not show albuminuria before the administration of the drug.—Slaughter (1896) reports symptoms of collapse in an individual following the administration of 20 grains in a pint of water. Biesenthal (1891; 1893), however, claims that large doses of 6 gm. cause no disturbance of renal function. In criticizing the report of Rörig, Biesenthal states that the picric acid reagent for albumin also gives a precipitate with piperazin which appears in urine after administration, and therefore is not characteristic. Bradford (1892) observed urticaria in a patient with gouty tendency following the ingestion of about 1 gm. of piperazin, but inasmuch as the individual complained of digestive disturbance and had also received phenacetin, salol and local applications it is apparent that no definite conclusions regarding piperazin alone can be made. Headache and some vomiting after doses of 2.5 gm. were experienced by Heubach (1891). In phloridzinized dogs piperazin completely inhibits the glycosuria, and after 14 days' treatment of a diabetic patient with 1 to 1.5 gm. doses (total 3), the sugar excretion fell from 8 to 3.3% (Hildebrandt, 1893). The activity of hydrolytic ferments was also found to be checked. Gruber (1893) reports similar results. Rabbits tolerate 0.5 to 1 gm. hypodermically according to Van der Klip (1892).—D. D. Stewart (1894) states that following the administration of 70 grains of the drug per day there were intermittent, clonic spasms of extremities, muscular prostration, incoherence, incoordination, tremors, and these symptoms disappeared 30 hours after onset. Tremor, malaise and nausea were observed with smaller doses. According to Wittzack (1893) subcutaneous injections of piperazin are painful. Wood (1902) claims to have observed muscular weakness and general depression following continuous exhibition of large doses. Therapeutic doses in man, however, produced no symptoms.—Van der Klip (1902) observed that sufficiently large doses of piperazin cause vomiting, irregular breathing, general muscular weakness and relaxation. The dissociation of oxygen from hemoglobin was lessened in a concentration of 1:5000; a 0.5% solution favored the coagulation of blood and the action of peptonizing ferments was checked. Bohland (1894) also claims piperazin lessens the oxygen liberating property of hemoglobin because the spectroscopic band of oxyhemoglobin remained unchanged for days and weeks. According to Bohland piperazin is also an antiseptic and causes hemolysis. On the other hand, Cushny (1910) states that piperazin seems to induce no symptoms in man or animals even when used in large quantities.

12. FATE AND EXCRETION OF PIPERAZIN.

This is of importance in connection with the therapeutic use of the drug as a urate solvent, for if piperazin is largely destroyed in its passage through the body, much could not be expected of its supposed solvent action in urine. According to Mordhorst (1898) excretion of the drug itself occurs in urine, but so much is destroyed that a considerable reduction of the concentration occurs in the body. Van der Klip (1892) detected the drug in 4 hours in rabbit's urine. Neubauer and Vogel (1898) state that the greater part of the drug is excreted in a few hours; the excretion lasts a few days, and the drug appears unchanged in the urine. According to Wood (1902) piperazin is rapidly absorbed and eliminated by the kidneys producing a reddish-brown urine. With the aid of the bismuth-iodide reagent, Helbing and Passmore (1894) claim to have determined that the greater part (11 grains) of 15 grains of piperazin was excreted unchanged. By means of the same reagent, Zimmermann (1901) demonstrated the presence of piperazin in the cloacal contents of a parrot. Biesenthal (1893) claims piperazin is excreted into the urine as such. Cushny (1910), however, states that but very little of the drug reappears in urine, and what escapes in this way is in combination with the stronger acids and not uric acid. Fraenkel (1906) states that piperazin passes unchanged in urine, and is excreted rather rapidly, oxidation also taking place. The opinion in general seems to be that piperazin is decomposed to a certain extent and bound with acids in the body, and in this way robbed of any activity it may possess (Poullsson, 1912; Heinz, 1907).

13. OTHER URATE SOLVENTS.

Lycetol.—Chemically this is dimethyl piperazin tartarate. Its structural formula is

The behavior of lycetol in the body differs in no particular from piperazin (Fraenkel, 1906). Anthony (1895) claimed beneficial results in 6 cases of gravel. However, in the absence of any data whatsoever, this report may be regarded as a mere testimonial. Basile (1901) observed that lycetol can dissolve added uric acid, but that it is variable, the differences being due to variable qualities of urine. Added to urine in the concentration of 1%, lycetol dissolved about 0.7% uric acid, whereas after administration, the excreted portion in urine dissolved only about 0.4%. Lycetol, therefore, loses considerable uric acid solvent power by passing through the body. So far as urate calculi are concerned, 1% lycetol dissolved about 0.15 to 0.25% of uric acid, but had only a weak effect on mixed calculi. Basile also studied the effects of the administration of lycetol to 26 patients and concluded as follows: Diuresis was augmented (from 910 to 1100 c.c.); gravel disappeared from urine; the quan-

tity of uric acid excreted remained small or uninfluenced in the beginning, but later was augmented; clinically the patients who suffered with "uric acid diathesis" became improved; the specific gravity of urine was not appreciably reduced; urinary acidity was diminished, some urines becoming neutral, others alkaline. Beneficial results in gout and sciatica are also claimed by Basile. While the relief in the various conditions was attributed by Basile chiefly to the urate solvent power of lycetol, this can hardly be the case altogether because of the small and uncertain uric acid values reported by him, the uncertainty of factors influencing this, and because of the possibility of spontaneous relief in these conditions without drugs. In much the same way may be regarded the symptomatic relief in gout and sciatica reported by De Tollenaere (1897).

Hoven (1898) reported beneficial results with 1 gm. of the drug in gouty individuals, and attributed this favorable action to increased alkalinity of the blood and urine, but these conclusions are not justified for lycetol alone because of the simultaneous use of other medication such as magnesia usta and liberal quantities of mineral water. 8.9% of added uric acid was dissolved by lycetol at room temperature as observed by Meisels (1902). However, the nature of the solvent (urine or water) is not stated in the only abstract available. Lycetol has no influence on the excretion of uric acid by birds with experimental gout (Waucomont, 1912). The clinical condition was also uninfluenced.

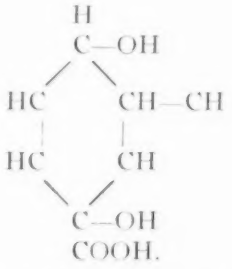
Sidonal.—This is a piperazin salt of quinic acid, called piperazin quinate and possesses the following chemical formula

$$NH\begin{matrix}/CH_2\ CH_2\backslash \\ \backslash CH_2\ CH_2/\end{matrix}NH\ .\ 2C_6H_7\ (OH)_4\ .\ COOH.$$

The effects on uric acid or urate should differ in no essential respect from the effects of the individual components, and this seems to be the case according to the reports in the literature. Bardet (1901) administered 3 to 5 gm. of the drug daily to 3 patients and observed its effect on diuresis, uric acid excretion and reaction of urine. It was found that these remained practically uninfluenced. According to Blumenthal (1900) the excretion of uric acid is reduced by 40 to 50% with daily injections of 5 to 8 gm. of the drug, and in place of uric acid, hippuric acid appears in the urine. Mylius (1900) makes a favorable report, unaccompanied by any data, on the use of sidonal in gout. Rosenthal (1900) reports that in a case of gout the administration of 100 gm. of sidonal led to the reduction of uric acid in urine from 0.75 gm. per liter to 0.332 gm. and that the tension of the skin over the tophi and redness disappeared. After a pause of 3 weeks, 100 gm. of sidonal was administered with similar improvement. This was repeated again in 3 months, and 6 months later the condition is said to have remained permanently improved. Klemperer (1900) is dubious about the therapeutic value of sidonal in gout because the value of piperazin has not been demonstrated and, in his experience, quinic acid is also worthless. The experiments of Foerster (1899) showed that the administration of sidonal (to six patients) causes no important differences in the excretion of uric acid. 10 to 25 gm. of the drug were used daily for 3

to 5 days using suitable controls. Foerster could not confirm the reported claims of his day, and pointed out that some other explanation for the reported effects must be sought rather than the drug itself. Meisels (1902) reports that sidonal dissolves 35.5% of added uric acid, but the temperature and solvent used are not stated in the only report available. Schlayer (1900) reports such beneficial effects as reduction in uric acid excretion from the administration of sidonal to 6 cases of "uric acid diathesis," increased diuresis, diminished turbidity of urine and lessening of renal pains in an individual with renal stone. Waucomont (1912) observed no beneficial effects on the clinical condition of experimental gout in birds.

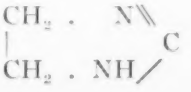
Quinic Acid.—This is closely related to benzoic and other aromatic acids. Its formula is



It has been recommended as a urate solvent, but its mode of action has remained unexplained. It has recently been shown by Denis (1915) that the administration of quinic acid has little or no effect on the uric acid content of urine or blood, leaving the threshold of the kidney for uric acid unaffected, and differing in this respect from salicylate and atophan. Likewise the information obtained from the literature referred to in this section, indicates that quinic acid possesses no special virtues as a urate solvent.

According to Cushny (1910) quinic acid has no effect whatever on the quantity of uric acid excreted. Foerster (1900) claimed to have demonstrated an increase in uric acid excretion, and urine output following the administration of a total of 50 gm. in several days. Unfortunately the results are complicated by the simultaneous administration of thymus gland. Fraenkel (1912) states that Weiss observed a diminution in uric acid excretion. Hupfer (1903), however, denies the lessening effect on uric acid excretion by quinic acid. The experiments of Meisels (1902) on pigeons with artificial urate deposits seem to indicate that quinic acid is less efficient than sidonal as an inhibitor of the deposits. In human individuals sidonal increased the excretion of uric acid from 0.3289 to 1.968 gm. Taltavall and Gies (1903) found that in dogs on constant diets, quinic acid (1 to 20 gm. in 10 days) did not affect the elimination of uric acid. This agrees with the observations of Hupfer on human individuals. This was further confirmed by Ulrici (1901), who also showed that quinic acid does not influence nitrogenous metabolism.

Lysidin.—Chemically this is ethylen-ethylen diamine, and the formula is



Lysidine is said to possess five times the solvent action of piperazin (Fraenkel 1912). According to Goodbody (1896), urine containing 0.1% of the drug increased the solution of urate in normal urine from 0.059% to 0.065%; the acidity was diminished from 0.35% to 0.33%. Following the administration of 1 gm. of lysidine daily for 8 days, and 2 gm. daily for 4 days, maintaining the diet, fluid intake, and exercise constant, Goodbody observed an increase in diuresis, increase in uric acid excretion, but no important changes in urinary reaction. In these particulars lysidine was found to excel piperazin. Haskins (1916) found that lysidin can act as a uric acid solvent (added uric acid) in acid urine. The urinary reaction may remain truly acid. If the urine is alkaline, when either lysidine or piperazin is administered, its uric acid solvent property is enhanced, but it is not a practical therapeutic agent because if large enough doses are used it is unsafe and possesses no advantage over sodium citrate or bicarbonate. Meisels (1902) observed that lysidin in aqueous solution can dissolve 47.86% of added uric acid. Meisels also observed that the administration of lysidine gave relief to pigeons with urate deposits. According to Neubauer and Vogel, Ladenburg (1894) claims lysidine urate is soluble in 6 parts of water.

Clinically, however, Ortner (1908) states he cannot recommend lysidine as a urate solvent, adding that "it not only has never done any good in my experience, but once, after a few days' use, it caused an almost general acute, painful, and partly bullous eczema." According to Schmiedeberg (1909) lysidine dissolves uric acid in vitro more easily than lithium carbonate, but the addition of 1% sodium chloride completely inhibits this. Favorable reports on the use of lysidine in gout and urate deposits are made by Wolf (1907). Lysidine is not regarded as an effective calculi solvent by Casper (1897). According to Ortowski (1900) lysidine is inferior to hexamethylenamine as a uric acid solvent. By the addition of uric acid to urine containing lysidine (0.5%), Tunicliffe and Rosenheim (1908) found the solvent power to be 33.2 when that of urine alone was expressed as 1. The solubility of sodium biurate in beef serum containing lysidine (0.1%) was 1:25,000 as compared with 1:60,000 in serum alone. The solvent power of piperidin was higher, 1:12,000.

Urol.—Chemically urol is a urea salt of quinic acid, (2 molecules of urea combining with 1 molecule of quinic acid), and according to Frieser (1902) is beneficial in gout, rendering the urine free of "uric acid excess." However, no data are offered to substantiate this vague claim.

Urosin (lithium quinate).—The administration of 10 to 25 gm. daily for 3 to 5 days produced no important differences in the excretion of uric acid, nitrogen and phosphate (Foerster, 1900). Foerster could not confirm the reported claims of other observers, such, for instance, as that of Weiss (1900), who claimed that urosin lessens uric acid formation because of its quinic acid content.

Salicylate.—The chemical formula for salicylic acid is $C_6 H_4$. OH. COOH. It has been frequently shown that the administration of salicylate increases the elimination of uric acid, but the mechanism of action has not been thoroughly understood. It has recently been shown by Denis (1915) that the ad-

ministration of salicylate leads to a diminution of uric acid in the blood with a simultaneous increase in the uric acid content of the urine, and this is interpreted as due to a lowering of the threshold of the kidney for uric acid excretion. The earlier literature has been abstracted in a previous contribution (Hanzlik, 1915) and need not be further detailed here.

Phenyl-quinoline.—The effects of a number of phenyl-quinolines on uric acid excretion were studied by Luzzatto and Ciusa (1913) with negative results. The most favorable results were obtained with diphenyl-quinoline carboxylic acid (atophan) and diapurin (a-phenyl-β-naphthoquinoline carboxylic acid).

It would be altogether out of place here to refer to the rather extensive literature on atophan. Other sources (Sollmann, 1917; Fraenkel, 1912) may be consulted for this. Briefly, however, it may be stated that atophan is related chemically and pharmacologically to salicylic acid. For lack of any other explanation it was generally held that atophan is a "mobilizer" of uric acid in the tissues. However, it has been shown by Folin and Lyman (1913) and Fine and Chace (1914) that the effects of atophan on the excretion of uric acid consists of an increased elimination in the urine with simultaneous decrease in the uric acid content of the blood. Haskins (1913) also observed that atophan increases the elimination of uric acid in the urine.

Colchicum.—This was found by Rockwood and Van Epps (1900) and Abl (1913) to decrease uric acid excretion. On the other hand, an increase in excretion was reported by Jackson and Blackfan (1907). Most recently, however, it has been shown by Denis (1915) that the administration of wine of colchicum exerts little or no influence on the uric acid content of the blood and urine.

*Piperidin.**—Tunicliffe (1897) found 50 c.c. of a 10% solution to completely dissolve 10 gm. of uric acid. The piperidin urate could be completely precipitated by sodium chloride and its solubility was found to be 5.3% and 25% at 17° and 36°, respectively. Aqueous solutions possessed an alkaline reaction. According to Tunicliffe his results do not confirm the high solvent power ascribed to piperidin urate by others.

14. SUMMARY.

There is no reliable evidence to show that piperazin, in small or therapeutic doses, imparts to urine urate solvent qualities, either by direct addition or after excretion.

Excessive doses of the drug produce a slight but practically negligible increase in uric acid excretion, the same being effectively secured by the use of such well known alkalies as bicarbonate and citrate.

The solvent action of low concentrations of piperazin on calculi is practically negligible. In very high concentrations a solvent power, though limited and doubtful, seems to exist.

There is no reliable evidence to indicate that piperazin can prevent or remove urate deposits.

*For description see foot note, Section 4.

Diuresis is uninfluenced by the administration of even large doses of piperazin.

The direct addition of piperazin to urine renders it alkaline. However, after administration the reaction remains unchanged because in its passage though the body enough piperazin is destroyed to markedly reduce its concentration in the urine.

Scientific evidence, though limited, and clinical opinion indicate that piperazin is valueless in gout.

The administration of piperazin may be attended with serious side actions.

There is sufficient scientific evidence to indicate the worthlessness of the following as urate solvents; urosin, lycetol, sidonal, quinic acid, lysidine, urol, quinoline, colchicum and piperidin.

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CHRONIC COLITIS AND ITS ROENTGENOLOGIC FINDINGS*

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THIS paper comprises a study of a group of cases of chronic colitis in which marked pathologic changes occur in the intestinal wall resulting in inflammatory thickening, contraction, granulation, or ulceration.

Chronic colitis is a disease that is constantly attracting more attention from both the medical and the surgical members of the profession. The number of patients affected with the disease is increasing, probably because the number of cures do not keep pace with the annual incidence of the disease. We have recently reviewed the cases of chronic colitis of this type in the Mayo Clinic in which a roentgen examination of the colon was made, and we wish to submit a résumé of the subject including certain roentgen findings that we believe are of particular importance and have not been sufficiently emphasized (Fig. 1).

The etiology in these cases of colitis is obscure. It is probably due to some constitutional derangement with a low grade of intoxication that seems to affect primarily the mucous lining of the large intestine, and at times, the terminal portion of the ileum. Chronic constipation probably plays a part as a predisposing factor but does not explain all. It may be due primarily to some specific organism upon which is superimposed considerable localized trauma, local irritation, and mixed infections. The rectum and sigmoid are first and always the most severely affected but eventually the process tends to become diffuse throughout the entire colon and occasionally the lower 12 to 24 inches of the terminal ileum. The early changes occur in the mucosa, which becomes reddened, thickened, and infiltrated with serum and blood cells. This chronic inflammatory reaction results in the formation of granulation tissue. The mucous glands are increased in number and hypertrophied, or they may become atrophic, small or cystic. The mucous folds are increased or decreased in number and lose their normal appearance. There is an overproduction and hypersecretion of mucus. Polypi and pedunculated papillomas may be formed. Localized superficial erosions and chronic ulcerations are frequently superimposed on all these changes, especially when there are polypi and papillomas, giving rise to deeper mixed infection and more profuse bleeding. In the severe and long standing cases localized abscesses and extensive tissue destruction of the mucosa and the submucosa complicate the disease. The remaining structures of the bowel wall undergo corresponding inflammatory changes and they may occur quite early. There is always an edema and lymphocytic infiltration and exudation in the other coats of the intestinal wall accompanying the changes in the mucosa. The coats are congested and thickened, multiple minute areas of scar tissue are formed, the bowel is contracted down, and is comparatively less yielding and less flexible (Fig. 2). Invariably the serosa is covered with a

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fibrinoplastic lymph exudate and becomes devoid of its normal luster. Frequently the peritoneal cavity contains a small amount of fluid and lymph.

The symptomatology is quite well known. There is usually a history of sea-

Fig. 1.—(106451.) Normal colon.

sonal spells of chronic diarrhea and spurious diarrhea, with five to twenty, or more, stools per day over a period of weeks or months at a time for many years. The stools usually are thin and watery and contain much mucus, occasionally purulent material, and at times, blood in varying amounts from a trace to

moderate or profuse quantities, depending on the duration and the severity of the disease. There may be traces of partially undigested food particles in the stools. There are intervals of complete or partial relief, during which time constipation may be present or the symptoms may be mild and more or less

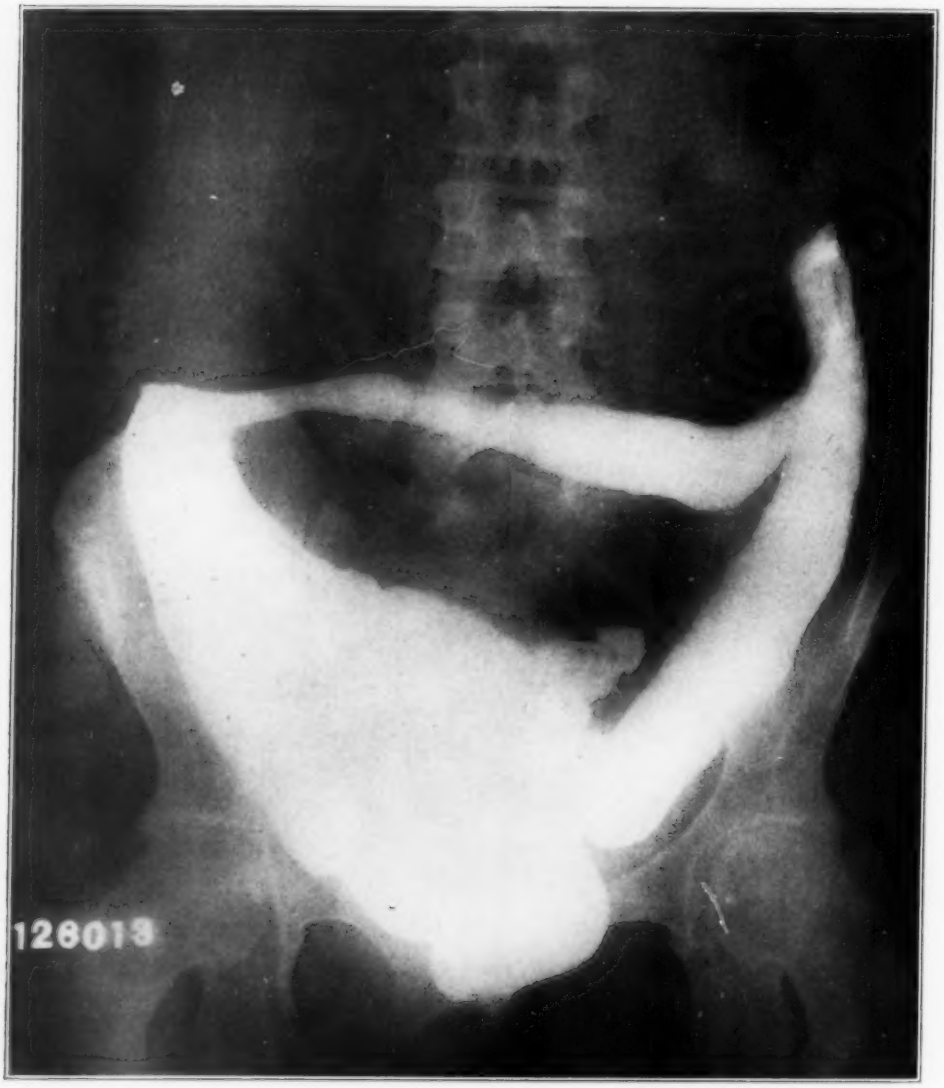

Fig. 2.—(126013.) Female, age 25 years. Chronic colitis of 8 years' duration. Roentgenogram shows a small smooth colon, with absence of haustra especially well marked from the hepatic flexure onward. Ileocecal valve incompetent.

continuous, with a history of acute exacerbations from time to time. The use of the coarser and irritating foods usually exaggerates the condition, and dietetic indiscretions often precipitate an attack. Pain and tenderness are often absent. When present they vary from a diffuse or localized abdominal soreness on pressure, to severe tenderness and marked muscular rigidity. The left lower quadrant

of the abdomen is the area most commonly affected, but this condition may be present over the course of the entire colon. Rectal tenesmus and pain at defecation are often distressing symptoms.

Loss of weight is common during severe attacks, but patients usually regain

Fig. 3.—(107128.) Male, age 54. Clinical diagnosis of chronic colitis of eleven years' duration. Roentgenogram shows a narrow, smooth, sausage-like colon. Both flexures ptosed. Incompetent ileocecal valve. No haustration seen.

in the intervals. In some cases the patient is surprisingly well nourished and well developed. Nausea and vomiting are unusual and the appetite is ordinarily very good. An acute attack may prove fatal in a few weeks or months from prostration, dessication, repeated intestinal hemorrhages, or from perforation of the bowel with general peritonitis.

In the event of other pronounced constitutional symptoms, or of the stools containing much blood, there is a moderate or severe grade of secondary anemia. There may be a slight leucocytosis, and in the presence of tissue destruction and mixed infection, there is always present an increase in the white blood count with a moderate predominance of polynuclear cells. Eosinophilia is rare. Digital examination of the rectum usually reveals a roughened and granular mucosa which is hypersensitive, painful, and bleeds easily. The anal sphincter is usually very spastic. The disease is resistant to almost all forms of medical treatment, although palliative measures may control the symptoms to a large extent for long periods of time. Spontaneous remissions are common in the milder stages and forms of the disease.

The incidence of the disease is slightly larger in males than in females, but there is very little difference, and the disease runs about the same clinical course in both sexes. Rural people and those living in the smaller towns appear to be more commonly affected. There seems to be no particular geographical distribution of the cases examined in the Mayo Clinic.

Repeated stool examinations are always essential as it is necessary to rule out the more common causes of chronic diarrhea. In these cases no intestinal parasites are found. It must be remembered, however, that in an entamebic colitis that has been treated with emetin, the stools may be free from parasites on several examinations and still some of the symptoms persist. Theoretically tuberculous and other specific bacterial infections can be identified by centrifugation of a small portion of the stool content and microscopic examination of properly stained smears. There is also usually a suggestive history and other symptoms and physical signs present in tuberculous and bacillary colitis cases. A history of luetic infection, other constitutional stigmata and the Wassermann reaction will put one on guard for the possibility of a syphilitic lesion in the lower part of the intestinal tract, although, of course, both conditions may be present. Fortunately syphilis of the rectum and colon is very rare.

The proctoscopic examination is an efficient aid in the differential diagnosis, and in ruling out a low-lying malignancy, either alone or superimposed on some other chronic process. Proctoscopic examination usually reveals a chronic indurative proctitis and sigmoiditis of a granular type which bleeds easily with few ulcerations irregularly distributed. Occasionally small polypi or papillomas may be seen. Frequently it is only by removing a small piece of suspicious tissue and subjecting it to careful microscopic examination that malignancy and the infectious granulomas of the rectum can reasonably be excluded.

Very little has been written concerning the signs elicited in the roentgen examination of chronic colitis, and no great importance has been attached to roentgenologic findings in this disease up to this time. In 1912 Schwarz,[1] of Vienna, described the characteristic features in a small number of cases of chronic colitis. Among other things he included the phenomena of a small and smooth bowel, absence of haustration and incompetence of the ileocecal valve (Fig. 3). We have found from an examination of a number of colons in chronic colitis that these conditions are invariably present and we believe that their importance should be emphasized. These roentgenologic phenomena are not due to spasm,

but result from the organic alterations in the bowel wall, because definite pathologic changes are found in both the gross and the microscopic appearance of all the coats. Furthermore, they are permanent and cannot be altered in their main appearances and characteristics by the administration of antispasmodics to physio-

Fig. 4.—(12716.) Female, age 57 years. History of chronic constipation and migraine for a period of twenty-five years. Roentgenogram shows marked redundancy of the colon. Incompetent ileocecal valve. The bowel is smooth and its outline is practically without haustration, but the colon is not contracted. Further the history distinguishes the case from a chronic colitis.

logic effect prior to a second roentgen examination. Besides, enterospasm has not been observed by us during the roentgen examination in this type of colitis.

There are certain other conditions of the large bowel in which some of these phenomena may also be found to a varying degree; but, as a rule, they can be

eliminated either by a correlation of the roentgen findings with the clinical data, or the roentgen picture alone may definitely indicate a lesion other than colitis. For example, in an occasional case of chronic constipation, the large bowel may be smooth and show no haustration (Fig. 4). Exceptionally also, in cancer of

Fig. 5.—(144665.) Female, age 44 years. Filling defect in the right half of the transverse colon. Roentgen diagnosis: Carcinoma. The remaining bowel is smooth and unhaustrated, but not contracted. The filling defect was produced by a carcinoma, as proved at operation.

the colon, the unaffected portion of the bowel may have smooth, unhaustrated borders (Fig. 5). However, these findings are not constant. In such instances the lack of haustration is doubtless due to relaxation of the longitudinal muscle bands—the tenia.

The incompetence of the ileocecal valve, which has been noted rather constantly in cases of chronic colitis, is not of itself diagnostically important, since we find it in a very high percentage of all cases examined, whether normal or pathologic. But, in conjunction with other roentgen signs of chronic colitis, it may have some corroborative value, when the barium runs into the ileum spontaneously and profusely.

It is worthy of note that in a limited number of cases examined of chronic endamebic colitis, we did not find a roentgenologic picture in any measure differing from the normal. The group included cases of long standing and of recent exacerbations but none that were prostrated. Sanford[2] has emphasized the fact that the entire syndrome of chronic endamebic colitis as seen in the North is not so severe as in the South and the tropics, which may explain the absence of marked pathologic changes in the bowel wall. However that may be, we believe that the roentgen examination offers distinct value in the differentiation of these two diseases, especially as seen in this latitude.

Our own experience suggests that the roentgen findings when carefully correlated with the clinical history can be made of much use in the diagnosis of chronic colitis. The roentgenogram also enables a more accurate estimate of the extent of involvement and thus may serve as a guide in determining whether the treatment shall be medical or surgical.

Both roentgenoscopy and roentgenography were employed in the cases herewith reported. The enema was preferred to the ingested meal. In an extensive chronic colitis of long standing the capacity of the colon is materially lessened. It fills very rapidly, and if the clyster is administered with much force the patient is very likely to expel it before the roentgen observations are completed.

The following illustrative cases were selected from the group studied:

Case 146817.—Male, aged 38; shoemaker. Registered November 30, 1915.

Previous History.—Pneumonia April, 1915.

Present Illness.—For 2 years spells of diarrhea with 15 to 20 stools per day of a thin watery character, with much mucus and at times blood stained; odor not offensive. With attacks there was loss of weight and strength. During the past four months, interval of but two weeks when he was free from severe symptoms, and during the past three months there has been considerable bright red blood in the stools, much abdominal cramp-like colic and rectal tenesmus. Never any chills or fever noted.

Physical Examination.—Considerable emaciation. Evidence of moderate anemia. Pyorrhea alveolaris and gingivitis present. Palpable liver margin. Slight tympanitis and slight diffuse abdominal tenderness. Digital examination of rectum negative.

Urinalysis.—Negative.

Blood Examination.—Hemoglobin 70 per cent; 4,520,000 red blood cells; 10,000 white blood cells; 38 per cent polymorphonuclear leucocytes; 44.3 small lymphocytes; 16.7 per cent large lymphocytes; 1.0 per cent eosinophiles. Wassermann, negative.

Stool Examination.—Red blood cells and pus cells present, no parasites found. Culture from stool negative for Shiga bacilli.

Roentgen Examination.—Colon, small and smooth throughout. No visible haustration. Ileocecal valve, incompetent. (Fig. 6.)

Clinical Diagnosis.—Chronic colitis; pyorrhea alveolaris and gingivitis.

Operative Findings.—Colon contracted to about caliber of small intestine, and presents appearance of a chronic inflammatory reaction with thickened and edematous walls, increasing in severity from cecum downward to rectum.

Operation.—Ileostomy (Brown)—Appendectomy secondary.

Case 134997.—Female, aged 33. Housewife. Registered September 13, 1915.

Previous History.—Negative.

Present Illness.—A 9 year history of chronic constipation with passage of some mucus in the stools, and at times blood tinged. For the past 2 years constipation has been more marked, requiring brisk laxatives or purgatives which in turn caused a diarrhea that re-

Fig. 6.—(146817.)

quired medicine to control. For the past 6 months she has complained of diarrhea and spurious diarrhea associated with the passing of mucus streaked with bright red blood, also cramp-like abdominal pains and rectal tenesmus. Normal weight 107 pounds, present weight 97 pounds.

Physical Examination.—Thin and pale in appearance. Marked intestinal peristalsis demonstrable. Digital examination of the rectum painful; rectal mucosa roughened and congested.

Urinalysis.—Negative.

Blood Examination.—Hemoglobin 60 per cent, 4,500,000 red blood cells, 14,400 white blood cells, and a normal differential count. The Wassermann was negative.

Stool Examination.—Red blood cells and pus cells present, no parasites found.

Proctoscopic Examination.—Chronic proctitis and sigmoiditis with some superficial ulcerations.

Fig. 7.—(134997.)

Roentgen Examination.—The left arm of the transverse colon, the splenic flexure, the descending colon, and the sigmoid are small, smooth, and unhaustrated. This condition was unchanged after the administration of an antispasmodic to physiologic effect. Note that the disease is limited to the left half of the large bowel as shown in the roentgenogram (Fig. 7).

Clinical Diagnosis.—Chronic ulcerative colitis.

Operative Findings.—Chronic ulcerative colitis.

Operation.—Ileostomy (Brown)—Appendectomy secondary.

Case 160059.—Female, aged 28. Clerk. Registered May 18, 1916.

Previous History.—Negative except appendectomy 10 years ago elsewhere.

Present Illness.—For 12 years she had had spells of diarrhea and bloody stools associated with loss of weight and strength. Some temporary relief with medical, dietetic, and local treatment. She has been without symptoms as long as a year at a time. At the present time there are from 6 to 8 stools daily, containing much blood and mucus and associated with considerable tenesmus.

Physical Examination.—Negative except for some tenderness over the entire colon and considerable tenderness on digital examination of rectum.

Urinalysis.—Negative.

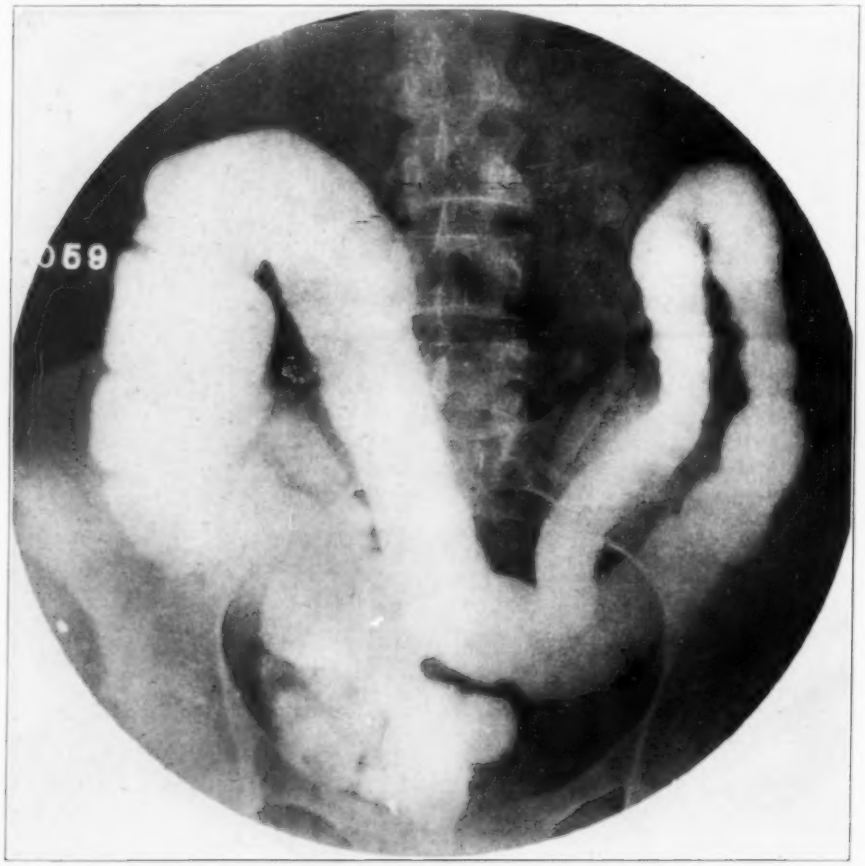

Fig. 8.—(160059.)

Blood Examination.—Hemoglobin 80 per cent.

Stool Examination.—Negative for parasites.

Proctoscopic Examination.—Examination very difficult on account of the contracted condition of the rectum. Marked proctitis which bleeds easily. No gross ulcerations. The sigmoid could not be examined on account of spasm.

Roentgen Examination.—Beginning at the hepatic flexure the colon was smooth, contracted and without haustral markings. The narrowing was most marked in the left half of the transverse colon, the descending colon and the sigmoid. The transverse colon was redundant. Ileocecal valve incompetent. (Fig. 8.)

Clinical Diagnosis.—Chronic granular colitis.

Operative Findings.—Granular type of chronic colitis. Definite thickening and nar-

rowing of the colon wall. Slight injection of its blood vessels. Appendix removed at former operation elsewhere.

Operation.—Ileostomy (Brown).

Autopsy.—General peritonitis. Colon showed chronic inflammatory changes with marked thickening throughout its entire wall and many petechial hemorrhages, old and recent, in its mucosa. No ulcerations. Small papilloma in the descending colon.

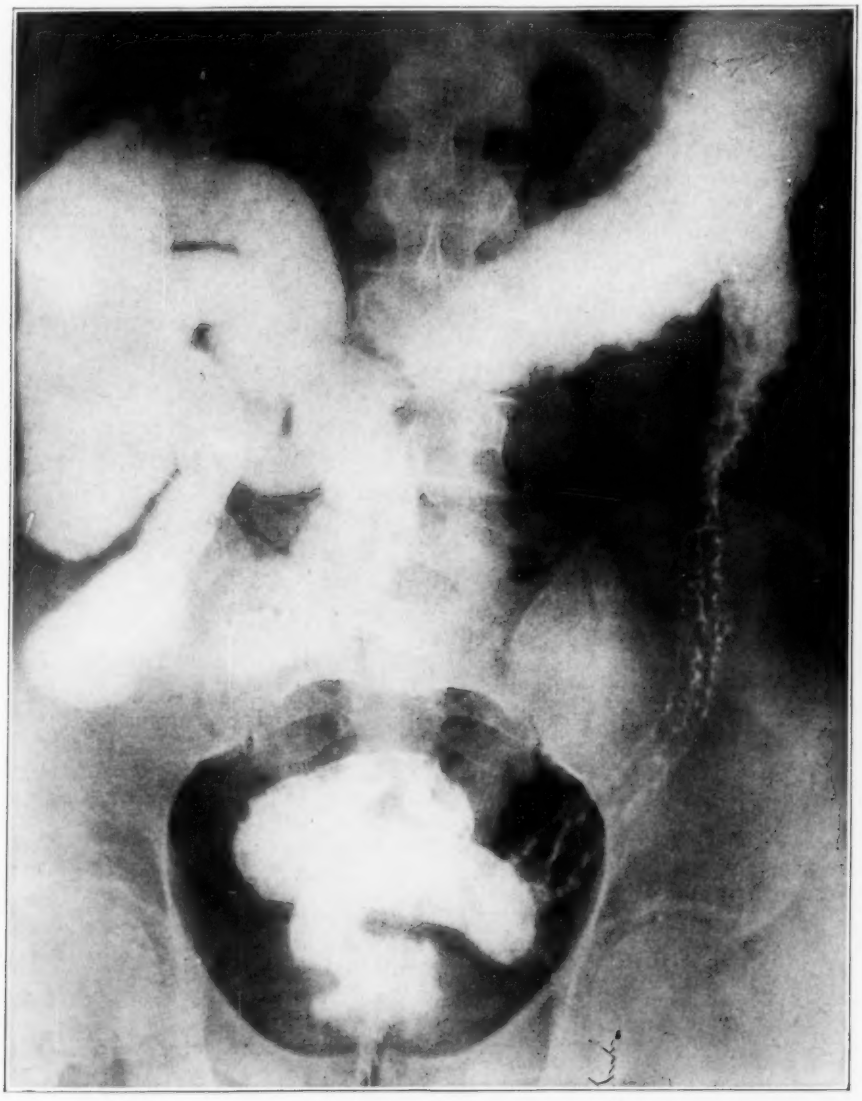

Fig. 9.—(172507.)

Case 172507.—Male, aged 35. Iowa farmer. Registered September 14, 1916.

Previous History.—Negative.

Present Illness.—For 3 years there have been spells of diarrhea with blood stained mucus in the stools, and associated with rectal tenesmus. The early spells were of about 6 weeks duration. Considerable loss of weight with each attack. During the past 14 months the symptoms have been practically continuous and the stools contained considerable blood. For

the bleeding he had a cauterization of the rectal mucosa elsewhere with practically no improvement. For the 3 weeks prior to admission to the clinic he had had 10 to 20 stools per day, containing much blood and mucus. History of slight fever at times during past month.

Physical Examination.—Twenty pounds loss of weight. Evidence of anemia. Slightly tender over entire abdomen. Digital examination of rectum painful and difficult.

Urinalysis.—Negative.

Blood Examination.—Marked secondary anemia with an average hemoglobin of 34 per cent. Wassermann negative.

Stool Examination.—Negative for parasites; red blood cells and pus cells present.

Proctoscopic Examination.—External and internal hemorrhoids were found but not sufficient to account for all symptoms. Large fissure into rectum. Indurated area in anterior wall of rectum 2 inches up.

Roentgen Examination.—Roentgenoscopy.—Entire colon smooth, contracted and without haustration. Roentgenogram (after involuntary partial evacuation).—Hepatic flexure, descending colon and sigmoid mottled in appearance; ileocecal valve incompetent (Fig. 9).

Clinical Diagnosis.—Fissure of rectum (postoperative), hemorrhoids; chronic ulcerative colitis; secondary anemia.

Fig. 10.—(172507.)

Clinical Notations.—Medical and dietetic treatment, and blood transfusion without improvement. Died 13 days after admission.

Autopsy.—Chronic inflammatory changes in the wall of the large bowel with marked diffuse edema and thickening of all its coats. The mucosa shows chronic ulcerations in the lower colon and rectum (Fig. 10).

CONCLUSIONS.

1. There is a group or chain of subjective and objective symptoms that is quite characteristic of chronic colitis.

2. There are definite organic changes in all the coats of the colon wall in chronic colitis, resulting from chronic inflammatory reaction with edema, lymphocytic infiltration, thickening, scar tissue formation, and contraction.

3. The roentgen examination in these cases shows the colon to be small, smooth and without haustration in the part or parts affected.

4. A more accurate estimate as to the extent and severity of the involvement can be obtained by a correlation of the clinical history with the roentgen findings.

5. The roentgenogram will frequently be an aid in determining the course of subsequent treatment.

6. In a limited number of examinations we have not found cases of chronic endamebic colitis which furnish any characteristic or similar roentgen findings. Therefore, it appears to be an aid in differentiating amebic from chronic colitis.

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CERTAIN ASPECTS OF PURULENT MENINGITIS*

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EPIDEMIC purulent meningitis due to infection with the diplococcus of Weichselbaum rarely offers great difficulty of diagnosis, and the acute purulent meningitis secondary to obvious infection of the middle ear or the air sinuses is as a rule recognized early and with ease. There are, however, certain cases such as the three which came to autopsy in this hospital but a few weeks apart which are in a different category. They present points of interest in etiology and in diagnosis since in these instances only one was recognized. The second and third were diagnosed, respectively, uremia and cerebral hemorrhage though the former showed only a moderately pathological kidney and the latter no trace of hemorrhage in the brain.

Oppenheim[1] discussing the etiology of this variety of meningitis names as reported etiological factors: streptococcus, staphylococcus, pneumococcus, pneumobacillus, bacillus typhosus, bacterium coli, bacillus lactis aerogenes and the bacillus influenzæ. The primary source of infection may be any acute infection, notably pneumonia, typhoid, ulcerative endocarditis, variola, acute rheumatic fever, influenza and gonorrhea, (?) or the condition may complicate a septicemia or a pyemia.

The clinical history and autopsy protocol are in abstract.

J. B., Hospital No. A-6688, was a white male machinist, aged 35. He was admitted to the hospital on October 8, 1916, complaining of pain in the right side on deep inspiration, chills and fever. The family history was negative. The patient denied the usual infections of childhood but admitted chancre at 20 and gonorrheal urethritis at 22. He averaged five glasses of whiskey and two of beer daily.

One week before admission he spent a day in the rain fishing. Five days later there was an acute onset with fever, chills, and pain in the right side on deep inspiration. About 24 hours later he began to cough up a brownish sputum. He sweated at night.

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On admission he was obstreperous and therefore in shackles. The chest was symmetrical and expansion was equal on the two sides but was rapid and labored and the patient was rather cyanotic. Vocal fremitus was increased over the right side of the back except at the extreme base where is was diminished. On percussion there was dullness over the right back and in the axilla. A few moist râles could be heard over the right back, and at the extreme base respiration was distant. The heart and abdomen are noted as clinically negative. The cervical glands were palpable and firm. There was marked pyorrhea alveolaris. The urine, except for a few hyaline and granular casts, was normal. The white count was 16,800.

Neurological examination showed moderately dilated pupils which reacted to both light and accommodation. The external ocular muscles functionated normally. The neck was not rigid. "The reflexes are normal—there is slight tremor" (of the hands?).

The history notes that the patient's delirium continued and that on the tenth day after admission he began to vomit and showed a suggestion of rigidity of the neck. On the seventeenth day after admission a radiograph of the chest was negative except for some slight clouding at the apices. On the eighteenth day paracentesis of the pericardium was attempted without obtaining fluid and on the same day lumbar puncture liberated 40 c.c. of cloudy fluid "under pressure." Cultures showed an organism which was "either the pneumococcus or the streptococcus viridans." During the period of hospital residence the temperature ranged between 100° and 102° F. and the pulse was slow in proportion (74 to 90) during the first week. The patient died on the twenty-first day after admission.

Clinical Diagnosis.—Pneumonia; cerebrospinal meningitis; chronic diffuse nephritis; pericarditis (?); acute endocarditis.

AUTOPSY PROTOCOL. (M. G.)

There was a paracentesis wound in the fifth costal interspace. Opening the pericardium liberated about 5 ounces of bloody fluid which came from a wound of the heart wall about one inch from the apex. The left side of the heart was hypertrophied and the musculature was generally edematous. There was a large mass of vegetations on the aortic cusps and surrounding cardiac muscle. The liver, spleen and kidneys were all congested and edematous and showed multiple infarcts. Very fine pleural adhesions prevented the collapse of the lungs on opening the thorax, but there was no excess of pleural fluid. The organs were edematous and of brick red color on section with areas of anthracosis. There were scars of old adhesions on the lower and middle right lobes. Neither lung was consolidated but crepitated throughout. The gastric mucosa was congested and edematous and the veins about the cardia much injected.

On removing the calvarium the brain was found to be bathed in pus and the cerebrospinal fluid purulent.

Anatomical Diagnosis.—Diffuse purulent meningitis; edema and congestion of liver, spleen and kidneys and gastrointestinal mucosa; pleuritic adhe-

sions; hypertrophy of left heart; acute vegetative aortic valvular endocarditis; cardiac apical wound with hemorrhage into the pericardial sac; acute splenic tumor; infarct of the liver and multiple infarcts of spleen and kidneys.

No focus of infection was found in the skull and it seems fair to trace it back to the aortic vegetations or even back to the pyorrhea. The multiple infarcts may well have been the result of infection. Without violating probability one may reconstruct the history as follows: pyorrheal infection at a remote date involving ultimately the liver, spleen, kidneys, and endocardium, and perhaps the pleura. Chronic alcoholic poisoning plus a day of exposure broke down the resistance and the infection became general. The very definite clinical signs in the lungs with rather inconsiderable pathological findings remains unclear. At what time the central nervous system became involved is doubtful. Delirium and fever coincided from the first, but in an alcoholic who presented such a classical picture of pneumonia the central nervous system was rather likely to escape attention. It is regrettable that lumbar puncture was not done before the onset of definite meningeal symptoms as either negative or positive findings would be an addition to the postmortem study of the case.

The differential diagnosis of acute purulent meningitis offers some difficulties particularly in the early stages when fever is not infrequently absent. Osler[2] reports the following case as typical of this difficulty. I have taken the liberty of abbreviating.

Male, aged 57. Had been drinking heavily and when admitted was delirious. His friends stated that he had been in this condition for a week. His temperature on admission was 97.5° and there was no symptom of meningitis. The case was regarded as delirium tremens until the fourth day when his temperature rose suddenly to 105°. He died two days later. Necropsy showed extensive yellowish purulent exudate over the hemispheres, turbid exudate at the base and along the Sylvian fissures and in excess in the ventricles. Direct smears showed a rounded coccus but the cultures yielded a diplobacillus. From the lungs which showed a slight bronchopneumonia, the diplococcus of pneumonia was recovered.

It is a platitude to remark that gastrointestinal conditions can produce in children a complex hardly distinguishable from meningitis, the so-called meningismus. The "wet brain,"—"serous meningitis,"—of alcoholics, which is probably an edema of the brain pure and simple, can simulate the febrile period of true meningitis accurately. Perhaps one would better say that the early stage of a meningitis which ultimately becomes purulent is serous. Luetic meningitis may occasionally have a course so acute as to give rise to confusion.[3] Major hysteria can, of course, simulate any disease one may discuss. Uremia is mentioned by most writers as capable of giving rise to difficulty. [1, 4, 5] However, all these conditions can be accurately differentiated by lumbar puncture and urinalysis. A mistake could have been avoided by this means in the following case.

The clinical history is brief and can be given in full. "The patient was admitted to the ward in a dying condition. Breathing stertorous. Pulse very feeble and irregular. The heart could not be heard owing to large râles over the chest. Eyes rolled upward and to the left. The patient had been catheterized

in the receiving ward and the urine found to contain much albumin. Coma was profound. Reflexes were abolished. The patient did not respond to stimulation. He died an hour after admission to the ward."

In abstract, the postmortem findings were as follows: The skull showed the evidence of an old trepanation—a lack of continuity about 5 cm. in diameter in the left temporal region. The dura was more than ordinarily adherent to both the skull and the pia, particularly along the longitudinal fissure. The brain showed the usual picture of acute purulent meningitis. The greatest accumulations of pus were over the parietal cortex of the vault and both the inferior and superior aspect of the frontal lobes, over the inner aspect of the temporal lobes, in the cisternæ and along the base of the cerebellum. The pituitary was almost completely destroyed by suppuration. Other than edema or cloudiness of the membranes of the posterior nares and the sphenoidal sinus, no focus of infection could be found in the head.

In the right hypogastrium there was an old apparently surgical scar through which hernia had occurred. The appendix was missing. The liver, spleen, stomach and intestines showed no important pathological change. The right heart was hypertrophied, the coronary vessels dilated as also to a slight extent the pulmonary and tricuspid orifices. There was hypertrophy of the ventricular wall and moderate (30 c.c.) effusion in the pericardium. The lungs showed some old fibrous pleural adhesions and marked edema. The kidneys were large and their capsule stripped with difficulty. The cut surface was pale and the cortex marked with lines of interlobular congestion. The cortex was thick and not well delimited from the medulla. There was slight papillary fibrosis. The brain showed the usual picture of acute purulent meningitis. Smears showed a mixed infection probably as a result of postmortem invasion—a large spore bearing bacillus, a small diplococcus (?) which was not intracellular, a slender polar stained bacillus and a rod-like form resembling the bacillus influenzæ. All were Gram-negative.

In this case the clinical diagnosis was uremia, yet postmortem there was not sufficient renal change to verify it. Lumbar puncture would have definitely settled this diagnosis.

A third case is of little clinical interest because of the inadequate examination and history and the entirely unwarranted diagnosis. Pathologically the case presents an unusual distribution.

Again the brevity of the history permits its presentation in full. "Admitted to the ward on a stretcher in a semi-comatose condition. Pupils reacted to light very little: conjunctival reflex absent: reflexes of the lower extremities present on both sides. No abdominal; no cremasteric reflex. No apparent difference in both extremities. Pulse good; heart normal; temperature 104°."

The clinical diagnosis was cerebral hemorrhage! In the abstract the autopsy protocol is as follows: The body of a well developed fairly obese negro of about 50 years. Pupils equal and moderately dilated. Marked pyorrhea alveolaris and slight evidence of herpes on the upper lip. There were old scars on both tibiæ. The apex of the right lung was adherent to the pleura, but there was no pleural effusion.

There was a slight increase of sub-epicardial fat and of pericardial fluid. The heart was somewhat enlarged, the right side hypertrophied and the musculature fibrotic. The mitral and tricuspid valves were somewhat thickened but like the other two were entirely competent. The aorta was dilated and contained fatty plaques with one area of calcification. The course of the (abdominal)? aorta showed multiple areas of subintimal hyaline thickening. The coronaries were somewhat tortuous but their ostia were patent. In the substance of the liver were numerous yellowish-white patches. The kidneys showed the usual picture of chronic interstitial fibrosis and some retention cysts. The spleen and pancreas were congested. The stomach was enormously distended and the superficial veins enlarged particularly at the cardiac end. There too the mucous membrane was tremendously congested. Other than a solitary petechial hemorrhage the mucous membrane of the intestines showed no im-

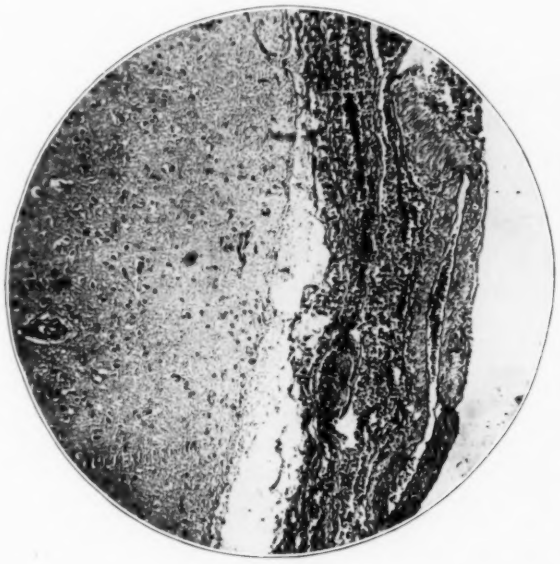

Fig. 1.

portant change but there were dense adhesions of the upper loops to themselves and of the sigmoid to itself and to the descending colon. There was moderate inflammation of the tip of the appendix.

When the calvarium was removed the dura was not unusually adherent. The basilar vessels were not sclerotic but there was marked cerebral congestion. The pia was generally edematous and showed multiple areas of opacity resembling exactly those seen in luetic meningitis, but microscopic section through these showed an acute purulent reaction. (Fig. 1.) Careful examination by coronal sections showed no trace of hemorrhage. There was no evidence of skull fracture.

The grounds for the diagnosis seem insecure. The patient lived twenty-four hours but no history was secured and the blood pressure is not recorded. There is no mention of hemiplegia or any other form of paralysis. In the

face of this and of the high temperature the diagnosis of hemorrhage is unwarranted. Cultures of the spinal fluid would have been of exceptional interest. Whether such slight degrees of inflammation could be detected in this way deserves investigation. It is to be noted that here too there was a marked pyorrhea and as in the first case this may have been the original source of infection.

All three of the writer's cases and that quoted from Osler came into medical hands in an abnormal mental state,—two in delirium and two with marked clouding of consciousness. Unless definitely contraindicated it would seem almost imperative to perform lumbar puncture on patients so received. Osler in the lecture quoted says: "During the past ten years no single measure of greater value in diagnosis has been introduced than Quincke's lumbar puncture." Of the three cases personally reported here, in the first an earlier puncture would have prevented the disastrous attempt at paracentesis of the pericardium: in the second, it would have corrected an absolutely erroneous diagnosis.

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LABORATORY METHODS

APPARATUS FOR USE IN EXAMINING FECES FOR EVIDENCES OF PARASITISM*

By Maurice C. Hall, Ph.D., D.V.M., Detroit, Mich.

In a previous paper,[1] later reissued with addenda,[2] the writer has given a comparative study of methods of examining feces for evidences of parasitism. In that study, the various methods which had been advocated were described and it was pointed out that these numerous modifications of technic had as their object the concentration of parasite eggs and the facilitation of the detection of the eggs or of other parasitic material, such as segments, entire worms, etc. Such concentration is obtained by taking advantage of the differences in physical, chemical, and biological properties between parasitic and nonparasitic material. These are mostly differences in specific gravity, size, physical, and chemical solubility, adhesiveness, and capacity for growth and development.

In comparative tests, the writer found the most satisfactory procedure to lie in the middle course between the old and crude smear method and the rather elaborate refinements which call in the use of various chemicals. Very dependable results were secured within a quite reasonable time by taking advantage of the purely physical differences existing between parasitic and nonparasitic material. These results were obtained by the use of screens to remove coarse material and use of a liberal amount of water to remove soluble coloring matters and fine matter in suspension. The use of some apparatus for breaking up fecal masses was advocated, and also the use of a centrifuge to save the time required for sedimentation of samples.

In the years since these studies were published, the writer has continued to find such a method as that outlined above quite satisfactory, but has found certain changes in the apparatus advantageous. The method I am using at present is as follows:

Rather large fecal samples, 2 or 3 ounces, are used wherever possible, instead of the classical sample, "about the size of a walnut." The reason for this is that in a general way it is desirable in our work to ascertain whether any parasites are present, not merely whether there is a massive infestation. By using large samples and concentrating the eggs present, it is possible to detect very light infestations. The use of the much simpler smear method, taking a small amount of fecal matter on the end of a toothpick and smearing it on a slide with a drop of water, will perhaps serve the purposes of the busy practitioner who cannot take the time and trouble to use more accurate methods, but it should be understood that the chance of detecting light infestations in this

*From the Research Laboratory, Parke, Davis and Company, Detroit, Mich.
[1]Bu. Anim. Indust. Bull. 135, 1911, 36 pp.
[2]Idem. with addenda, 1912, 42 pp.

way is much less than where the more elaborate methods are used. Where a physician is primarily concerned with detection of massive infestation with hookworm, the smear method will probably serve very well, especially since there will be clinical indications of such infestations in nearly all cases. But even here it should be noted that in communities where there are massive infestations with hookworm, there will usually be simple or combined infestations with ascarids, whipworms, *Strongyloides* or tapeworm also present, and it is desirable to detect these even in light infestations. Ascarids are regarded as rather innocuous by some physicians, but the writer would prefer an infestation with a moderate amount of hookworms to an infestation with ascarids in any amount from one up. The large size and wandering habits of these worms make them a potential source of serious danger. Cases have been reported where these worms have entered the ducts of the liver and pancreas, crawled up the esophagus and down the trachea to the lungs, or through the eustachian tube and out of the ear; where a single worm has caused enterospasm necessitating operative relief; where they have perforated the intestine and caused peritonitis; and even the not uncommon occurrence of vomiting one or more of these worms, which are about the size of a lead pencil, is a prospect one might well face with hesitancy. In view of these facts it would seem as well worth while to employ means to ascertain with the greatest possible accuracy whether worms were present, as to employ the utmost accuracy to ascertain whether *Plasmodium* or *Treponema* or *gonococcus* or *B. tuberculosis* were present. In any case accurate information is the thing sought.

Large fecal samples are also desirable for the reason that tapeworm infestation is not uncommonly present without eggs being present in the feces. It occasionally happens that segments of tapeworms are present and can be detected by using large samples and screening, and that the same fecal sample will show no tapeworm eggs owing to the fact that the segments have not ruptured and released the eggs. This is less apt to be the case for infestation with *Tænia,* owing to the position of the uterus in that species, though it is a possibility there also, but is not uncommonly the case for such cestodes as *Dipylidium,* where the eggs are retained in egg capsules in the parenchyma of the segment. In addition to tapeworm segments, the screens will occasionally retain entire nematodes or cestodes which are being passed, and of course the same would be true for flukes.

In the method previously given for fecal examinations, the writer described the use of a "milk shaker," of the type where the glasses are shaken up and down, for use in breaking up fecal samples. This apparatus, motor-driven, was very satisfactory in most respects, but had the disadvantage of being very noisy. A substitute for this machine was found in the newer type of mixer, in which a small motor drives a vertical shaft terminating at the bottom in a smooth-edged hexagonal disk. In this machine, which is shown at the right of Fig. 1, the motor head is lowered so that the disk is near the bottom of the inside of the bottle containing the feces, the current automatically turning on and spinning the shaft and disk as the motor head is lowered. This machine seems to be an improvement over the old type for breaking up feces. It works more

rapidly and is practically noiseless. It does not damage nematodes or isolated tapeworm segments which may be present, though it does sometimes break tapeworm strobilæ which may be in the feces. For the purpose of breaking feces to release contained worm eggs, it gives entire satisfaction. The old shaking machine worked with the bottle corked and was odorless in operation. The new machine works with the bottle uncorked, and does release unpleasant gases, but we have carried a rubber tube from the suction pipe in the laboratory and terminated the tube in a small funnel, shown in the illustration, which is held by rubber bands near and above the mouth of the bottle, and find that the suction serves to carry away practically all of the odors. The bottles used have a capacity of 400 mils, and water is added to the feces to make the total content about 300 mils.

The feces having been thoroughly disintegrated with the mixer, they are next poured through a set of sieves. In my former papers I described a sieve made by soldering brass screening to round tin pans from which the tin bottoms had been cut out except for a flange to which the screen was soldered. In the addenda, I noted that Dr. Cobb, of the United States Department of Agriculture had devised some oblong screens which he had found satisfactory. In making up screens for work here, the round form was abandoned and a screen which is approximately square was made up in the shops. These screens, shown in Fig. 1, are of copper, with inside dimensions about 7⅞ inches (20 cm.) square. They are made of two copper strips, swaged together at two diagonal corners, the top half inch of the metal being bent over and doubled back against the side on two opposite sides to form a reinforced rim, and being bent out and back on the other two sides to form a reinforced flange which carries the sieve in a rack. This flange is ¼ inch wide. The copper sides are two inches high. On the bottom of the sieves the metal is bent in to form a flange ⅜ inch wide for the attachment of the brass screening, which is soldered to this flange. The screens used have mesh apertures of 6, 8, 10, 14, 16, 20, 60, 100 and 120 to the inch, the latter being about the finest screen that will permit of the passage of the eggs of practically any worm parasite. Each sieve has a number stamped in the front side showing the number of mesh apertures to the inch in its screening. A solid-bottomed copper pan, of the same shape and dimensions as the screens, completes this part of the equipment.

In previous publications, the writer has advocated the use of a set of screens which could be "nested," and which were used in this fashion; the feces were poured through the screen when the latter were set one within another in proper order in a glass dish. While still in the service of the United States Bureau of Animal Industry, I abandoned this plan in favor of the use of a rack, similiar to the right hand one of the two racks shown in Fig. 1, constructed with two solid board sides and with the boards grooved so that the edges of the circular pans could be slipped into the grooves. The same type of rack serves even better with the present rectangular sieves, and has been improved in the left hand rack shown in Fig. 1, which is a skeleton construction, lighter and less inclined to warp. This latter rack is made of four upright wooden pieces joined by a series of transverse pieces on the sides and back, and

by a top and bottom piece in front. In examining feces for eggs, this large rack, with a carrying capacity of nine sieves and one solid-bottomed pan, is used, the coarsest screen being at the top and the pan at the bottom. When examining feces for worms passed after the administration of anthelmintics, the smaller rack, with an equipment of six of the coarser screens, using the 60 mesh for the bottom screen to guard against the escape of any worms, is used. The racks serve as storage containers for the sieves and pan when these are not in use.

When examining feces for evidences of parasitism in the shape of eggs or larger material, the feces broken up by the mixer are poured through the set of screens in the large rack and the screened feces collected in the pan. The screens are washed by running clear water through them until the pan is perhaps half full. This pan has a capacity of two liters. Then the pan is pulled

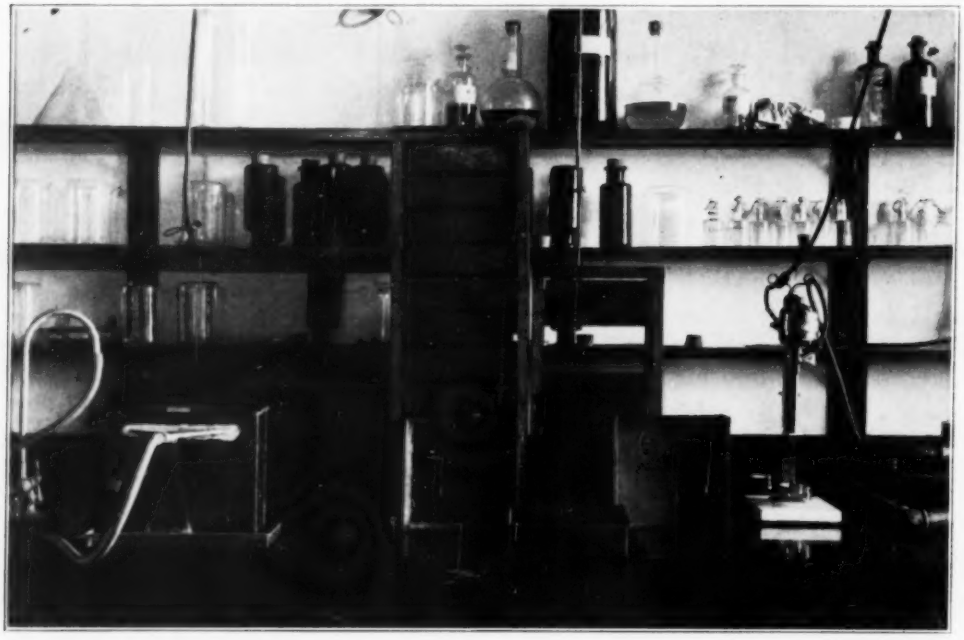

Fig. 1.—Apparatus for comminuting and screening feces, and for washing screens.

out and the contents decanted, sedimented, washed and centrifuged to suit the convenience and desires of the operator. The end result is a slide on which there is a minimum of foreign matter, and this foreign matter and the eggs alike are washed clean and stand out for just what they are in the clean water from which soluble matter and fine suspended matter have been removed. Such a slide can be examined with a maximum certainty of detecting eggs present and with a minimum amount of eye strain.

After the pan is taken from the rack, the remaining sieves are washed by running water through from the top until the water from the last sieve comes away clean; in other words until all the soluble coloring matter and matter fine enough to pass the screens are removed. Then the sieves are examined one at a time in a glass tray of clean water. Parasitic and nonparasitic matter are

now washed clean and appear in their true shapes and colors. There is little likelihood of mistaking vegetable or animal material for worms, and little likelihood of overlooking worms. Substantially the same thing is accomplished in examining feces with the smaller rack and fewer screens to detect worms passed after anthelmintics.

It is necessary that a screen equipment of this sort be kept clean and free from contamination that would give misleading results. To cut down the work of cleaning these screens, the apparatus shown at the left of Fig. 1 was constructed. This is essentially a copper box, 3½ inches wide, 9 inches high, and

Fig. 2.—Exterior view of dark cell for microscopic work.

10 inches long; just large enough to wash one screen at a time. Water is sprayed in through the fan shaped nozzle at the back, the aperture being cut down by solder plugs at intervals to increase the force of the water. On the front of this box are three overflow lips at the top and a small tube at the bottom; light material floats off through the upper lips, and heavy material, such as sand, is washed out at the bottom. The box is provided with a lid to prevent splashing and is set in a tray to drain any overflow to the sink. In practice, sieves are first rinsed under the overflow and then put in the box. One sieve is washed while the next is being examined. By using very hot water, the sieves are not only

cleansed, but practically sterilized. The mixer is very easily cleaned by holding a damp cloth against the shaft or disk while these are spinning.

So far as sterilization is concerned, however, it is advisable to have formaldehyde, a coal-tar disinfectant, or some other adequate disinfectant, added to the original fecal sample whenever feasible. This is valuable for sterilization and also aids in abating the odor. Where plenty of water is used, the odor is a matter of small moment, as the substances responsible for it are soon washed away.

The writer has long been in sympathy with Dr. Cobb's idea that in doing

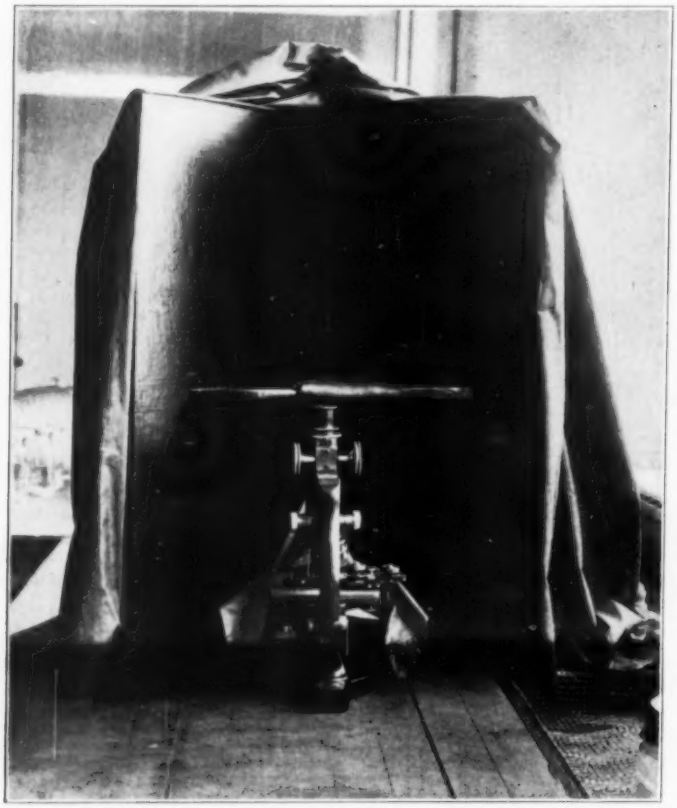

Fig. 3.—Interior view of dark cell for microscopic work.

microscopic work it was advisable to illuminate only the object under the microscope and to cut out, as far as possible, the illumination of the microscope and other extraneous objects in the room. However, the equipment which Dr. Cobb has used to attain his object is rather expensive, the cost of equipping each window with the very satisfactory apparatus which he has devised being about $80.00 to $100.00 two years ago, and probably more now. A similar result may be attained by the use of the simple and inexpensive device which is shown in Figs. 2 and 3. This device consists of two boards, each 2 feet long and 1 foot wide, joined at a right angle along the long edges by screws. As shown in Fig.

2, the boards are sawed out at the bottom of this right-angled union to a height of 8 inches, and a reinforcing board fastened along the bottom of the large boards and across the bottom of this aperture to prevent the structure from falling. To further prevent falling, the angle formed by these reinforcing boards is held under a bent nail. A strip of black cloth (lining) is nailed to the edges of the aperture and carried back to the stage of the microscope, permitting light to fall on the mirror. A large piece of black cloth (lining) is nailed to the free edges and top of the large boards, and when this is dropped over the microscopist, it forms a dark chamber which is very restful to the eyes in examining fecal samples for parasite eggs. Midway between the top and bottom of the boards is a triangular shelf, about a foot long on its free edge, and with the free edge hollowed out, beveled and padded to make a head rest. The woodwork of the entire interior of the dark cell is painted black. With this very simple and cheap device, one can examine fecal samples for hours and feel very little of the neck and eye strain that would result from the same amount of work in the open and with the head unsupported. There is only a certain amount of nervous energy available for work; and if this energy is partly dissipated in unprofitable strain on the neck and eyes and in the distraction incidental to seeing the objects and action in the room, there is that much less available for concentration on the work in hand. The use of this apparatus gives a distinct sense of concentration and a feeling of greater satisfaction in what otherwise quickly becomes rather tedious work. As Dr. Cobb has pointed out in his papers,' few microscopists seem to appreciate the value of providing suitable and comfortable conditions under which to work, but this does not detract from that value.

When the cloth at the aperture for illumination of the microscope mirror is pushed down and the cloth at the top and back of the dark chamber dropped, the microscope is covered and protected. This arrangement gives adequate protection to the instrument and is handier than the use of a microscope case, as the microscope is always in place ready for use.

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EDITORIALS

Complement Fixation in Tuberculosis

LABORATORY methods for the early diagnosis of pulmonary tuberculosis have been discussed in this journal, and especially that of complement fixation.[1]

The recently issued Transactions of the Twelfth Annual Meeting of the National Association for the Study and Prevention of Tuberculosis contain articles on this subject from various American laboratories. (Corper, Petroff, Meyer, Bronfenbrenner.)

Many workers in different countries have been busy endeavoring to find an antigen suitable and reliable for this test. As Craig relates, it was the study of Wassermann and Bruck upon complement fixation in tuberculosis that led to the possibility of working out such a test in the diagnosis of syphilis; yet up to the present time, no method of complement fixation in the diagnosis of tuberculosis has been generally accepted.[2]

Corper in a brief review of the literature states that Widal and Lesourd in 1901 were the first to demonstrate deviation of complement in tuberculosis. Bordet and Gengou on whose early observations these serological tests are based

demonstrated in 1903 tuberculosis antibody in the sera of tuberculous animals.

The great difficulty in the practical application of this test has been the inability to discover and to agree upon a suitable antigen.

In the above mentioned series of papers each worker has apparently developed his own type of antigen.

Petroff thinks there may be more than one antibody present in the blood stream, one antibody may react to a protein antigen while a second antibody will react to a lipoid antigen. For this reason Petroff devised different antigens, lipoid, and protein.

Dielman[3] and Much[4] have advocated the use of partial antigens.

Bronfenbrenner and Schlessinger found different samples of Besredka's antigen, although identical in preparation, differed in the amount of lipoids they contained. These workers state that it is necessary to free all antigen from lipoids by separating the protein fraction by precipitation before employing it as antigen.

The early experiments with old tuberculin or even with tubercle emulsion as antigen gave very uncertain results.

Calmette and Massol,[5] in 1912, devised a water and peptone soluble antigen which gave most reliable results, 92.5% of known tuberculous sera yielding positive tests.

Many investigators have followed Besredka's methods, using as antigen a filtrate of an egg meat broth medium on which tubercle bacilli have grown for several weeks.

This antigen, however, has been shown to yield complete binding in a somewhat large percentage of syphilitic sera, a fault of manifest objection to its usage.

Some investigators such as McIntosh, Fildes, and Radcliffe conclude that the antigen must contain living bacilli.

Zinsser and Miller have developed an antigen prepared by triturating living or dead bacilli with dry crystals of sodium chloride then adding distilled water up to isotonicity. This idea would seem to be founded on earlier observations by Gay.[6]

With this antigen the claim is made that cross fixation with luetic sera is eliminated, and that in a large number of cases of tuberculosis the results have been accurate in over 90% of the sera studied. Also by the tests made with this antigen the degree of activity of the disease may be measured.

Such claims may prove of far reaching importance both for the diagnosis and for the prognosis of tuberculosis. E. R. Baldwin,[7] however, is not yet prepared to accept these tests as of value in the diagnosis of tuberculosis although conceding their value for confirmation. He regards their results regarding prognosis as corroborative of the findings of clinicians, in that patients who have apparently arrested pulmonary tuberculosis should not consider themselves out of danger for several years to come; the complement fixation test being usually positive many months after apparent cure, and only gradually returning to negative.

We have employed several antigens in a series of several hundred cases

of pulmonary tuberculosis including early and late types. Those of Calmette and Massol, and of Zinsser and Miller have appeared reliable.

These cases have all been carefully controlled by clinical examinations and by x-ray plates. The results so far would appear to support the claims of the originators of these antigens; that the complement fixation test in pulmonary tuberculosis at least is most satisfactory both for diagnosis and for prognosis. We have rarely seen cross fixation with luetic sera and we feel that in this test we have a serological examination as valuable in pulmonary tuberculosis as the Wassermann reaction in syphilis. Just as in this disease the serum is set up to several antigens, so it would seem best not to rely on only one antigen in tubercle fixation.

The cutaneous tuberculin reactions are, as we know, still positive—denoting a hypersusceptibility—when tuberculous foci are healed, whereas we find the complement fixation test to be negative under these conditions.

Only a vast number of cases can finally settle the value of this reaction. The specificity of the reaction with the recently introduced antigens would seem to be settled.

The varying methods of preparing these antigens, by autolysis, by salt extraction, and by Petroff's method may, in time, be shown to have arrived at a common end in the production of a reliable antigen.

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—*G. B. W.*

Hunger and Appetite

A RATIONAL guidance of the desire for food and means for stimulating or controlling the appetite in pathological states can be obtained only when a knowledge of the determining factors of hunger are known.

Professor A. J. Carlson, of the University of Chicago, has been very fortunate in having in his service a young man, who on account of a complete stricture in his esophagus, has a permanent gastric fistula. The fistula is large enough to allow direct observation of changes taking place in the stomach, and to permit the insertion of various instruments. Prompted, no doubt, by the opportunity which such a subject offers for the study of gastric function, Dr. Carlson and his pupils have conducted an extensive series of researches upon the cause and control of hunger and appetite, and have extended these investigations to include observations upon normal and pathological individuals and upon animals under various experimental conditions. The results of these re-

searches have been recently summarized by Dr. Carlson in a book entitled *"The Control of Hunger in Health and Disease."** Any clinician who is interested in gastric disease should not fail to read the volume.

Carlson shows that the normal empty stomach is continually undergoing changes in muscle tone; and, superimposed upon these small contractions, there occur periodically strong contractions of the gastric musculature, which other observers have shown to be simultaneous with the sensation of hunger. These contractions the author calls "hunger contractions," and the period during which they occur, "the hunger period." A high degree of tone in the gastric muscle may be accompanied by a dull sensation of hunger, but it is only during periods when the contractions are strong that the actual pains of hunger occur. The contractions at the beginning of the hunger period are feeble and of slow rhythm, but gradually become more and more rapid and intense, with a corresponding increase in the hunger sensation.

Because Carlson has experienced the sensation of hunger during the contraction of the stomach which follows a sudden distention of its walls, he concludes that the contraction in some way initiates the afferent nerve impulse which gives rise to hunger. He was unable to produce hunger by any form of stimulation of the gastric mucosa, the esophagus, or the intestines.

The author found that during the hunger period there is a great increase in the reflex excitability. Perhaps this may explain the old saying, "cross and hungry as a bear," and also the cause of some of the sensory phenomena which are experienced by many people during hunger. During the hunger period the pulse rate and blood pressure are usually increased. This change may explain the relief of some headache following the taking of food.

Dr. Carlson was unable to produce the sensation of pain by any form of stimulation of the gastric mucosa, short of actual destruction of the cells and nerve endings. He suggests that pain produced in this way, or that occurring in some types of gastritis where even water or gastric juice cause pain, may be due to over stimulation of nerve fibers other than those of "protopathic" pain. Whether such pain is, as Hertz believes, due to hyperperistalsis, or to the actual injury to the gastric mucosa cannot be determined from the present evidence. The only physiological pain from the stomach evidently is hunger pain. Any other pain indicates a pathological process, or the stimulation of hyperexcitable stomach nerves. All attempts to demonstrate any tactile receptors in the mucosa met with failure, but protopathic temperature sense was found to be present.

Some people complain of nausea when they are hungry, and of being hungry when they are nauseated. Dr. Carlson believes that the sensations are not alike. Hunger involves the kinesthetic nerves of the stomach, while nausea of gastric origin is due to stimulation of the nerves of the mucosa. He thinks, however, that under certain conditions, as in persons with hyperexcitable vagi, strong hunger may actually pass into nausea.

The feeling of satiety following a full meal appears to involve several fac-

*Carlson, Autox J.: The Control of Hunger in Health and Disease. University of Chicago Press, Chicago, 1916.

tors, none of which depend upon the nerves of the gastric mucosa. The sensation of fullness, accompanied by the memory of taste and smell of food are all required to give this feeling.

The author considers appetite and hunger entirely different sensations. Hunger is produced by the contraction of the muscle of the stomach and the resulting stimulation of receptors in the muscle coats. Appetite, he believes to be primarily dependent upon past experiences with food, a pleasant memory of which is essential. Apparently appetite is a special complex case of the general desire for pleasure, which is modified somewhat by a gastric element. This latter element he demonstrates by placing chemical substances too dilute to cause pain or discomfort, such as alcohol, mustard, pepper, etc., into the stomach. He finds that these affect the consciousness in an opposite sense to pain, and in a way possibly identified with appetite. If such substances are introduced into the stomach without stimulating the taste or olfactory nerves, a sensation akin to the "coming appetite" experienced by normal individuals when eating is experienced.

Such substances introduced during a hunger period abolishes the sense of hunger and gives rise to a pleasant feeling accompanied by thoughts of the dinner table. It is a very significant fact that normal gastric juice, having full acid strength, is capable of giving this sensation. Gastric juice weaker than this abolishes the hunger contractions, but fails to excite what we may provisionally call the gastric element of appetite.

Carlson concludes that the process of feeding is an inherited instinct; a reflex which becomes augmented by the hunger state. In support of this conclusion he finds evidence in the fact that the hungry babe puts everything to its mouth. Experience soon teaches it that food removes the pains of hunger, and gives it pleasure. It, therefore, associates the food with the hunger pains, and its appetite with the pleasure experienced in eating.

Of interest especially to pediatricians are the experiments conducted by Carlson upon the hunger mechanism in babes. These showed that the infant's stomach, immediately after eating, is relatively quiet, but as the stomach empties, feeble tonus contractions appear which increase in rate and activity until, two or three hours after nursing, they end in typical hunger contractions. If food is at hand, infants eat when the hunger sensation is strong enough to make them uncomfortable and usually thrive upon this procedure. If the presence of hunger contractions is biological evidence that the stomach is ready to receive food, the editor wonders if the long pauses between feeding insisted upon by one school of pediatricians is not a rather doubtful means of improving nature.

The author found that the contractions of hunger are much stronger in the young stomach than in the old. That this is not due to the decrease in the metabolism is shown by the fact that even during starvation, when the hunger contractions are augmented, the old stomach never shows the same strength of contractions that the young one does.

The author and one of his pupils investigated on themselves the effect of a fast of five days' duration upon the hunger mechanism. During the fast in both cases there was no decrease in the gastric tonus or in the hunger contractions.

The sensation of hunger was weaker at the end of the period than one would expect from the intensity of the hunger contractions. The appetite increased somewhat on the first days of the fast, but on the last two days it decreased. This weakening of the hunger sensation and the appetite may be due to a depressed cerebral activity at this time. Upon breaking the fast, all the mental depression and much of the weakness disappeared at once. The second day after the fast Dr. Carlson states that he felt as if he had returned from a month's vacation in the mountains, and was able to do an unusually large amount of work. This observation is in keeping with McCullom's statement that periods of increased growth and improved body metabolism follow a fast in animals. The author remarks that the discomforts of starvation were greatest the first two days, but at no time did they amount to actual suffering. He also says that voluntary starvation cannot be considered a heroic act, and that starvation experiments on animals in the interest of science cannot be called cruelty.

Numerous experiments were made to determine the relationship of the nervous system to hunger. These showed that hunger contractions occur in decerebrate animals and during deep sleep, and that they are not under the control of the will. If the hungry individual's attention is directed to other things, the lesser contractions do not affect consciousness, but the more intense ones do, save during deep sleep and at times of exceptional mental activity. Habits of eating do not modify the occurrence of these contractions. Hunger is felt when the stomach is empty, and the body requires food. The sight of food increases the appetite, but does not increase the strength of the contractions in a starving stomach. Carlson found that stimuli received through the gustatory, olfactory, or gastric mucosa nerves, in no case augmented the hunger contractions, but when these stimuli were effectual at all, inhibition resulted, the inhibition, on the whole, being proportional to the strength of the stimulus.

The stomach, completely isolated from its nerve supply, still exhibits hunger contractions although they are modified in strength and rhythm. If the splanchnics alone are severed, psychic stimulation, which usually causes inhibition, no longer has as marked an effect as normally. The cutting of the vagi leaves the stomach in a hypotonic state, but the hunger contractions still persist with alterations in rate, rhythm, and strength. Some intestinal states inhibit the contractions, a fact which may give an explanation of the absence of hunger in many cases of appendicitis, gall stones, etc. The paths by which the augmentary and inhibitory stimuli which affect the hunger contractions reach the brain or the connections which they make in the cerebral cortex with the motor nerves of the stomach have not been determined. Dr. Carlson points out that such work must be accomplished by the clinician, since means for such investigation are not within reach of the physiologist.

Carlson investigated the hunger contractions in conditions known to increase the hunger sensations—such as pancreatic diabetes, phlorhizin diabetes, the hunger following profound hemorrhage and prolonged starvation. In all these conditions he discovered hunger contractions of great intensity. The blood from dogs suffering from the conditions injected into normal dogs during a period of hunger contraction augmented the existing contractions, but

if injected during a nonhunger period, no effect could be demonstrated. The blood apparently contains a harmone under these conditions, which stimulates contractions when the inhibitory factors are weak. The relationship which such a harmone plays is not clear, for, as Carlson points out, it is difficult to account for the periodicity and the abrupt termination which characterize the hunger contractions during a fast on the basis of a hunger harmone secreted by the tissues.

The results of Carlson's researches lead one to believe that the hunger contractions arise automatically within the neuromuscular apparatus of the stomach. The exact stimulus which initiates them is questionable; perhaps a harmone secreted by the tissues or the lack of tension on the walls of the stomach play a role. The movements are modified by the extrinsic gastric nerves in a way analogous to the control which the cardiac nerves have upon the heart.

Alterations in the hunger sensation are known to occur in many pathological conditions. Carlson found that the polyphagia of pancreatic diabetes was accompanied by abnormally strong hunger contractions. Dogs suffering with the mange have big appetites, suffer from the cold, and show very intense hunger contractions. Gastritis, induced in dogs by the administration of large doses of alcohol, caused a suspension of hunger contractions for a day or so. The gastric contractions as well as the desire for food returned, however, before the dogs were able to retain food without vomiting. In these cases hunger and nausea were both present. Distemper, pneumonia, and peritonitis all caused an inhibition of the gastric tonus. Artificial pyloric constriction in the dog caused a great increase in the contractions, and a hyperperistalsis of the stomach. These phenomena are similar to those observed in man with pyloric obstruction.

Patients suffering with diabetes, gastric cancer, and neurasthenia referred to the stomach, all showed abnormally intense gastric contractions. The pains of gastric ulcer apparently arise from hunger contractions, not abnormally increased, but perceived as more painful than hunger pains because of the hyperexcitability of the nerve fibers in the stomach. The gastric pain occurring in gall bladder disease some time after a meal, is probably due to rhythmical contractions of the gall bladder parallel with the hunger contractions of the stomach. In high fevers the hunger mechanism is inhibited.

—*R. G. P.*

Arteriosclerosis

CERTAINLY a large proportion of the vascular lesions one sees, especially those in the aorta, is of infectious origin, judging from the microscopic appearances. That is to say, they are typically inflammatory lesions which originate in the media about the vasa vasorum. There is, however, a large number of cases in which these inflammatory lesions are absent, but in which there are evidences of degenerative changes which are represented by fatty plaques and streaks showing through the intima, and others in which the lesions are merely productive ones affecting the intima itself. Practically all investigators who

have endeavored to produce vascular lesions, experimentally, with bacteria, have succeeded in causing inflammatory lesions associated with, in many cases, degenerative changes. Those who have used adrenalin have produced only degenerative lesions.

Bailey[1] has experimented with a toxin—that of the diphtheria bacillus—which he has used in sublethal doses over different periods of time, and studied the effects upon the vascular system and the kidneys of rabbits. In order to discover the relation of high blood pressure, he has used pituitrin in combination with the toxin in one series. Pituitrin was used because it produces no vascular lesions. He has been able to produce, with large doses of toxin, a vascular degeneration involving the entire aorta, the carotids to the base of the skull, the subclavians and iliacs, and, for a varying distance distally, the brachials, femorals, and large abdominal vessels. In combination with pituitrin extensive calcification occurred, due, Bailey believes, to the production of more extreme fatty degeneration. In the kidneys the toxin produced a pronounced vascular and parenchymatous degeneration.

Bailey remarks that the experiments do not show the effects of frequently repeated small doses, and it strikes one that this is what should be shown if the application is to be valuable. An individual does not, during disease, get a large dose of toxin at 10 A. M., and then none for another day or more. He is poisoned by more or less *continuous* absorption of toxic materials which are produced in gradually increasing amounts and then in gradually decreasing amounts. In diphtheria, the course of the disease is short and the period of absorption is brief; in typhoid, the course is longer; in intestinal stasis, it may be very protracted—but in all it is continuous.

The thing that Bailey's work is useful to demonstrate is that a certain type (degenerative) of arteriosclerosis is not microbic—not infectious—in origin, but toxic, and that the lesions may be produced by concentrated materials.

[1]Bailey: Jour. Exper. Med., 1917, xxv, 109.

—*P. G. W.*

Thymus

A VERY considerable amount of experimental work has been done upon the thymus, the object of it being to discover whether or not this organ has any important place in the economy of the organism. A large part of this work has been carried out with guinea pigs—the normal laboratory animal. The results have been contradictory. For instance, since 1845 when Restelli performed his first experiments, major reports have been made by more than twenty-five investigators on at least fourteen species of animals. Some have been able to see no results of removal and have inferred that the thymus has either no function in post-fetal life or that none can be demonstrated. Others have seen changes of a transitory character develop and consequently have thought that the thymus exercises a transitory function corresponding to its

own life history. Still others have determined that removal of the thymus is followed by symptoms and pathological changes of a profound character, culminating in death, and have drawn the conclusion that the thymus is essential to life.

A recent communication by Park[1] has to do with a new series of experiments in which the guinea pig was used. In this communication one very striking observation was made which upsets, to say the least, a large amount of previous work. Park found that accessory lobes of thymus derived from the third thyro-pharyngeal pouch, occurring in close association with the parathyroid from the third pouch, were present in the cervical tissue of 11 out of 14 guinea pigs. He believes that the same conditions would have been found in all 14 but for technical errors. In some animals other additional lobes of thymus tissue were found at some distance from the main lobe. The almost impossibility of complete thymectomy without disturbance of other cervical organs is made obvious by these observations, and the previous extirpation experiments of former workers must be discarded.

In Park's animals in which a complete extirpation seemed to have been accomplished, no physiologic effects were observed.

Park recalls that Basch is authority for the statement that herbivora are poor subjects for this sort of experiment, because, very early in these animals, bone has a high calcium content, which acts in a protective manner against the influences that result from cessation of thymus function. And yet it is well known that rickets occurs spontaneously in herbivora, and numerous investigators have reported changes in the skeleton of the rabbit following thymectomy, and one (Klose) has obtained rachitic-like changes in goats. No one, however, has succeeded in producing alterations in the skeleton of the guinea pig by thymectomy. If, as Park says, Basch's observation is true, that removal of the thymus is less apt to be followed by bone changes in herbivora than in omnivora or carnivora, another explanation is that extirpation of the thymus in the former is almost invariably incomplete.

All this recalls the lack of agreement concerning the cause of "thymus death." If Park's observations are true, and especially if they are extended to other groups of animals, then the mechanical cause in these cases must be conceded to be the essential one.

[1]Park: Jour. Exper. Med., 1917, xxv, 129.

—*P. G. W.*

The So-called Much-Weiss Tubercle Granules

MARMOREK, in 1900, noticed that young tubercle bacilli were often not acid-fast. E. Klebs,[1] a few years later, according to Ravenel, published confirmatory and more extensive observations.

In 1907 Much,[2] by means of a modified Gram's stain, demonstrated two non-acid-fast forms of tubercle bacilli. Almost simultaneously Michaelides[3] published somewhat similar findings.

Meader,[4] in a very thorough review of the literature concerning tubercle bacilli not stainable by Ziehl, discusses the clinical significance of what are now known as the Müch-Weiss granules and granular organisms. It is assumed that these may be degenerate types of tubercle bacilli and are non-acid-fast because of the absence of the wax coating.

Fishberg,[5] on the evidence and arguments presented by different investigators, accepts the probability that a diagnosis of pulmonary tuberculosis can be made on the findings of these granules when acid-fast bacilli cannot be discovered in sputum.

There has always been some difficulty in easily demonstrating tubercle bacilli in the pus from cold abscesses, in the discharges from tuberculous ears, in the contents of many tuberculous lymph nodes, and in the drainage from sinuses such as rectal fistulæ. It is claimed that in such conditions the Müch-Weiss granules are especially liable to be discovered.

Some experimentations on guinea pigs would appear to have been carried out to prove that these granules can produce tuberculosis following their inoculation. It must be borne in mind, however, that very few genuine virulent bacilli (less than ten) can infect a guinea pig when injected subcutaneously and that these few bacilli may easily have been overlooked in smears from such discharges.

With all the favorable arguments of different workers, enough animal inoculations have not been carried out and this corroborative evidence is especially lacking in a majority of the reports presented. Neither would it appear that sufficient evidence has been presented from postmortem examinations.

The report of Fraenkel and Müch[6] that identical granule forms are to be found in the glands of Hodgkins' disease and of lymphatic leukemia structures, would hardly seem to strengthen the theory that these granules stained in this manner are really tubercle bacilli.

In our own investigations we have so far failed to infect guinea pigs with the sputum in which the Müch-Weiss granules have alone been demonstrated. On the other hand, with large amounts of sputa repeatedly found negative to the Ziehl staining type of tubercle bacillus and in which these Gram positive granules were never discovered, we were able after several trials to infect a guinea pig and the true nature of the disease was determined.

Postmortem evidence is of even greater value. A man of 60, with persistent fever for several years, was pronounced a case of pulmonary tuberculosis by several eminent clinicians. All clinical signs were certainly typical of this disease. Very many examinations of the sputa failed to reveal Ziehl staining tubercle bacilli. The Müch granules were repeatedly demonstrated by the Weiss double stain. Guinea pig inoculations were negative. The case came to autopsy. Not a trace of tubercle infection could be anywhere detected. The case was one of chronic interstitial pneumonia.

Until more convincing evidence is reported of corroboration by guinea pig inoculation and by postmortem proof, it could hardly seem justifiable to render a diagnosis of pulmonary tuberculosis by the finding of these Müch-Weiss granules in the sputum of suspected cases.

What the exact nature of these granules may prove to be, it is impossible to surmise. It is to be remembered in such investigations that, if possible, two or three ounces of sputum are to be concentrated and treated and finally reduced to a very small centrifugated sediment. The method is laborious and very time consuming and cannot at this time be recommended.

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—*G. B. W.*